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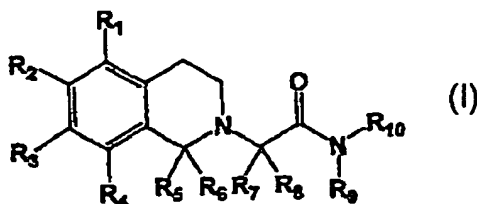
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(54) Title: 1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES



(57) Abstract: The invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivatives of formula (I) and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as orexin receptor antagonists.

## 1,2,3,4-Tetrahydroisoquinoline Derivatives

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The present invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivatives of the general formula I and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula I, and especially their use as orexin receptor antagonists.

10

The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: the orexin A (OX-A) (a 33 aminoacid peptide) and the orexin B (OX-B) (a 28 aminoacid peptide) (Sakurai T. *et al.*, Cell, 1998, 92, 573-585). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior (Sakurai T. *et al.*, Cell, 1998, 15 92, 573-585). On the other hand, it was also proposed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcoleptic patients (Chemelli R.M. *et al.*, Cell, 1999, 98, 437-451). Two orexin receptors have been cloned and characterized in mammals which belong to the G-protein coupled receptor superfamily (Sakurai T. *et al.*, Cell, 1998, 92, 573-585), the orexin-1 receptor (OX<sub>1</sub>) 20 which is selective for OX-A and the orexin-2 receptor (OX<sub>2</sub>) which is capable to bind OX-A as well as OX-B.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions such as pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive 25 neurosis; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; feeding disorders such as anorexia, bulimia, cachexia and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's 30 disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric dyskinesia; gastric ulcer; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; pituitary growth hormone;

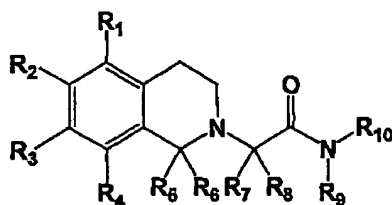
adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone  
5 deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke;  
10 subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV,  
15 post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders including nosological entities such as  
20 disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders and other diseases related to orexin.

The present invention provides 1,2,3,4-tetrahydroisoquinoline derivatives which are non-peptide antagonists of human orexin receptors, in particular  $OX_1$  receptors. In particular, these compounds are of potential use in the treatment of obesity and/or sleep  
25 disorders.

So far not much is known about low molecular weight compounds which have a potential to antagonise either specifically  $OX_1$  or  $OX_2$  or both receptors at the same time. Recently WO 9909024 has been published wherein phenylurea and phenylthiourea derivatives as  $OX_1$  antagonists are disclosed. Also quite recently WO 9958533 has been  
30 published disclosing the same type of compounds which are again

described as being preferably OX<sub>1</sub> receptor antagonists. The novel compounds of the present invention belong to an entirely different class of low molecular weight compounds as compared to all prior art orexin receptor antagonists so far published.

- 5           The present invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivatives of the general formula (I).



10

Formula (I)

wherein:

15

- $R^1, R^2, R^3, R^4$  independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclylalkyloxy,  $R^{11}CO-$ ,  $NR^{12}R^{13}CO-$ ,  $R^{12}R^{13}N-$ ,  $R^{11}OOC-$ ,  $R^{11}SO_2NH-$  or  $R^{14}CO-NH-$  or  $R^2$  and  $R^3$  together as well as  $R^1$  and  $R^2$  together and  $R^3$  and  $R^4$  together may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms;

20

- $R^5, R^6, R^7, R^8, R^9, R^{10}$  independently represent hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

25

- $R^{11}$  represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;  $R^{12}$  and  $R^{13}$  independently represent hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

30

R<sup>14</sup> represents alkyl, aryl, cycloalkyl, heterocyclyl, R<sup>12</sup>R<sup>13</sup>N- or R<sup>11</sup>O-.

The compounds of formula I can contain one or more asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers,  
5 diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

In the present description the term "lower alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1-5 carbon atoms. Examples of  
10 straight-chain and branched C<sub>1</sub>-C<sub>8</sub> alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, isobutyl, tert-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl, ethyl, propyl, isopropyl, butyl, 2-butyl, tert-butyl and pentyl.

15

The term "lower alkenyl", alone or in combination, signifies a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms, preferably allyl and vinyl.

The term "lower alkoxy", alone or in combination, signifies a group of the  
20 formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy, preferably methoxy and ethoxy.

Lower alkenyloxy groups are preferably vinyloxy and allyloxy.

25 The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C<sub>3</sub>-C<sub>8</sub> cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl, cyclohexyl and particularly cyclohexyl or lower alkyl substituted cycloalkyl which may preferably be substituted

30

with lower alkyl such as methyl-cyclopropyl, dimethyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl, methyl-cyclohexyl, dimethyl-cyclohexyl,

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group  
5 which optionally carries one or more substituents, preferably one or two substituents,  
each independently selected from cyano, halogen, hydroxy, lower alkyl, lower alkenyl,  
lower alkoxy, lower alkenyloxy, nitro, trifluoromethyl, trifluoromethoxy, amino,  
carboxy and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-tert-butoxyphenyl, 4-  
fluorophenyl, 2-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl and 2-naphthyl. Preferred  
10 are carboxyphenyl, lower alkoxy-phenyl, hydroxyphenyl and particularly phenyl.

The term "aralkyl", alone or in combination, signifies an alkyl or cycloalkyl  
group as previously defined in which one hydrogen atom has been replaced by an aryl  
15 group as previously defined. Preferred are benzyl and benzyl substituted in the phenyl  
ring with hydroxy, lower alkyl, lower alkoxy or halogen preferably chlorine.  
Particularly preferred is benzyl.

For the term "heterocyclyl" and "heterocyclyl-lower alkyl", the heterocyclyl  
20 group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may  
be saturated, partially unsaturated or aromatic containing for example 1, 2 or 3  
heteroatoms selected from oxygen, nitrogen and sulphur which may be the same or  
different. Example of such heterocyclyl groups are pyrrolidinyl, piperidinyl,  
piperazinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl,  
25 isoquinolyl, thienyl, thiazolyl, isothiazolyl, furyl, imidazolyl, pyrazolyl, pyrrolyl,  
indazolyl, indolyl, isoindolyl, isoxazolyl, oxazolyl, quinoxalinyl, phthalazinyl,  
cinnolinyl, dihydropyrrolyl, pyrrolidinyl, isobenzofuranyl, tetrahydrofuranyl,

30

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5 dihydropyranyl. The heterocyclyl group may have up to 5, preferably 1, 2 or 3 optional substituents. Examples of suitable substituents include halogen, lower alkyl, amino, nitro, cyano, hydroxy, lower alkoxy, carboxy and lower alkyloxy-carbonyls.

10 The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably chlorine and bromine and particularly chlorine.

The term "carboxy", alone or in combination, signifies a -COOH group.

15 A group of preferred compounds according to the present invention are compounds of formula (I) wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup> and R<sup>9</sup> are hydrogen. Examples of preferred compounds are:

20 2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-(cyclopropyl-methoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

25 2-[1-(3,4-dimethoxy-benzyl)-8-(2-fluoro-ethoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-(2,2-difluoro-ethoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-ethoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

35 2-[1-(3,4-dimethoxy-benzyl)-8-propoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

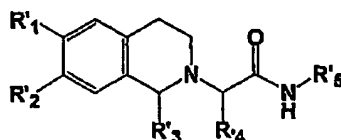
2-[1-(3,4-dimethoxy-benzyl)-8-allyloxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-isopropoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

- 5 2-[1-(3,4-dimethoxy-benzyl)-5-propoxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:



- 10 Another group of preferred compounds according to the present invention are compounds of formula (II)



General formula II

15

wherein:

- 18  $R'^1$  and  $R'^2$  independently represent hydrogen, hydroxy, alkoxy, heteroaryloxy, carbamoyloxy or halogen or may form with the phenyl ring a five, six or seven membered ring containing one or two oxygen atoms,

20  $R'^3$ ,  $R'^4$ ,  $R'^5$  independently represent aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl.

- The compounds of formula (II) can contain one or more asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for  
25 example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

Examples of preferred compounds of formula (II) are:

30

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide



- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
naphthalen-1-ylmethyl-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
5 (2-methoxy-benzyl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(4-fluoro-benzyl)-acetamide
- 10 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(6-methoxy-naphthalen-2-ylmethyl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(4-methoxy-naphthalen-2-ylmethyl)-acetamide
- 15 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(3,6)-difluoro-benzyl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
20 (1-phenyl-ethyl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(pyridin-3-ylmethyl)-acetamide
- 25 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(2-methyl-benzyl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(3-methyl-benzyl)-acetamide
- 30 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
35 (1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(pyrazin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-  
2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(thiazol-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
5 *N*-(5-methoxy-indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(6-methoxy-indan-1-yl)-acetamide

10 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(6-methyl-indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide

15 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(4-methyl-indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-  
20 methoxy-indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-  
methyl-indan-1-yl)-acetamide

25 2-{1-[4-(pyrimidin-2-yloxy)-3-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl}-*N*-benzyl-acetamide

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(*N,N*-dimethylcarbamoyloxy)-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

30 2-[1-(3,4-dimethoxy-benzyl)-7-(3-fluoro-propoxy)-6-methoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(2-fluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-  
35 2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(2,2-difluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

5 2-[1-(3,4-dimethoxy-benzyl)-7-(but-2-oxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(cyclopropyl-methoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

10 2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

15 2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

20 2-[1-(3,4-dimethoxy-benzyl)-7-isopropoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(1-methyl-prop-2-oxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

25 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

30 2-[(1*S*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide

35 2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

5 2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

*N*-benzyl-2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetamide

10 2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide

*N*-benzyl-2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetamide

15 2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide

20 2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide

2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-4-yl-methyl)-acetamide

25 2-[1-(3,4-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide

30 Examples of particularly preferred compounds of formula (II) are:

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

35 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-naphthalen-1-ylmethyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-

(indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide

5

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(pyrazin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-  
2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(thiazol-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-

10

2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(5-methoxy-indan-1-yl)-acetamide

15

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(6-methoxy-indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(6-methyl-indan-1-yl)-acetamide

20

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-

25

*N*-(4-methyl-indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-  
methoxy-indan-1-yl)-acetamide

30

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-  
methyl-indan-1-yl)-acetamide

2-[1-[4-(pyrimidin-2-yloxy)-3-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-benzyl-acetamide

35

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(*N,N*-dimethylcarbamoyloxy)-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(3-fluoro-propoxy)-6-methoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(2-fluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-  
5 2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(2,2-difluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

10 2-[1-(3,4-dimethoxy-benzyl)-7-(but-2-oxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(cyclopropyl-methoxy)-6-methoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

15 2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
20 (indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(indan-1-yl)-acetamide

25 2-[1-(3,4-dimethoxy-benzyl)-7-isopropoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(1-methyl-prop-2-oxy)-6-methoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-benzyl-acetamide

30 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-[(1*S*)-indan-1-yl]-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
35 *N*-benzyl-acetamide

2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
[(1S)-indan-1-yl]-acetamide

5 2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
benzyl-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
benzyl-acetamide

10 2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
benzyl-acetamide

*N*-benzyl-2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
acetamide

15 2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1S)-  
indan-1-yl]-acetamide

*N*-benzyl-2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
20 acetamide

2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-  
methyl)-acetamide

25 2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-  
methyl)-acetamide

2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-4-yl-  
methyl)-acetamide

30 2-[1-(3,4-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-  
yl-methyl)-acetamide

35 Examples of physiologically usable or pharmaceutically acceptable salts of the  
compounds of formula (I) are salts with physiologically compatible mineral acids such  
as hydrochloric acid, sulphuric or phosphoric acid; or with organic acids such as

methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula (I) with free carboxy groups can also form salts with physiologically compatible bases.

5 Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammonium salts such as Na, K, Ca or tetraalkylammonium salt. The compounds of formula (I) can also be present in the form of a zwitterion.

10 The compounds of formula (I) can contain several asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates and the meso-forms.

15 Preferred compounds as described above have  $IC_{50}$  values below 1000 nM; especially preferred compounds have  $IC_{50}$  values below 100 nM which have been determined with the FLIPR (Fluorometric Imaging Plates Reader) method described in the beginning of the experimental section.

20 The compounds of the general formula (I) and their pharmaceutically usable salts can be used for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity, diabetes, prolactinoma, narcolepsy, insomnia, sleep apnea, parasomnia, depression; anxiety, addictions, 25 schizophrenia and dementia.

The compounds of formula (I) and their pharmaceutically usable salts are particularly useful for the treatment of obesity and sleep disorders.

30 The compounds of formula (I) and their pharmaceutically usable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in 35 the form of suppositories). However, the administration can also be effected



parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

5 The compounds of formula (I) and their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules.

10 Suitable adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

15

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

20 Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or  
25 antioxidants. They can also contain still other therapeutically valuable substances. The invention also relates to processes for the preparation of compounds of Formula I.

The compounds of general formula (I) of the present invention are prepared according to the general sequence of reactions outlined in the schemes below, wherein  
30  $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^{10}$  are as defined in formula (I) above. As the case may be any compound obtained with one or more optically active carbon atom may be resolved into pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates and the meso-forms in a manner known per se.

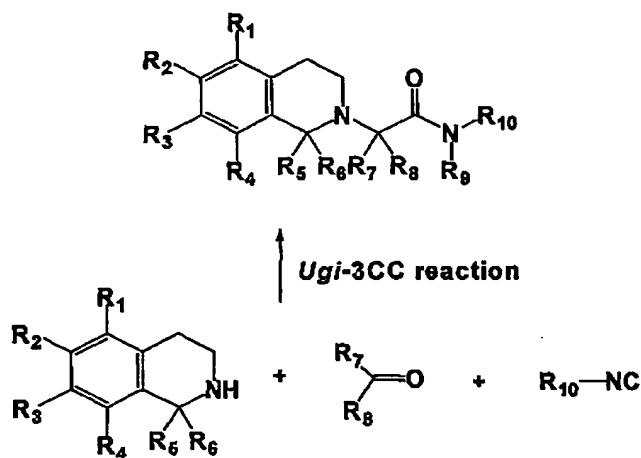
The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known per se.

The compounds of formula (I) may be prepared as single compounds or as  
5 libraries of compounds comprising at least 2, e.g. 5 to 1000 compounds of formula (I).

Compound libraries may be prepared by a combinatorial approach or by multiple parallel synthesis using solution phase chemistry.

10 For the combinatorial approach, the compounds of general formula (I) wherein  $R^6$ ,  $R^7$ ,  $R^9$  are hydrogen, are prepared using an Ugi-three-components-condensation reaction (Ugi-3-CC) which involves the one-pot reaction between a 1,2,3,4-tetrahydroisoquinoline derivative, an aldehyde and an isocyanide (*Scheme 1*).

15



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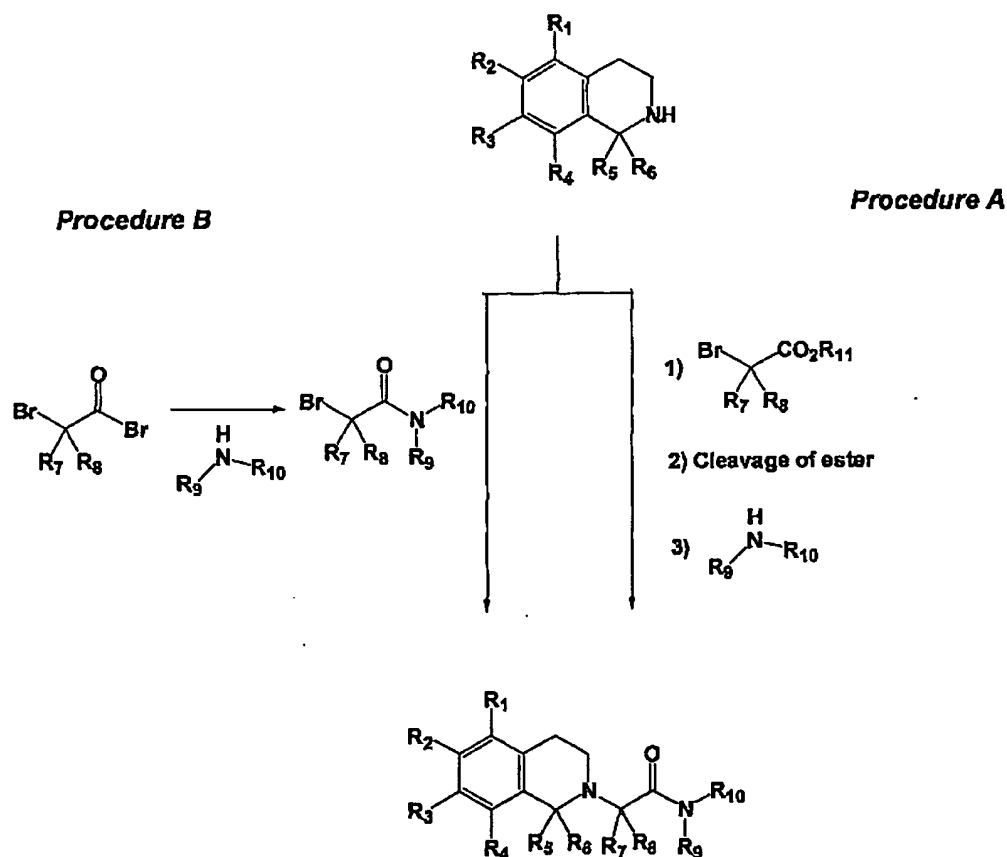
*Scheme 1*

25

Isocyanides not commercially available might be prepared from the corresponding amines by N-formylation followed by treatment with  $\text{POCl}_3$  (see e.g. J. March, fourth edition, Wiley-Interscience publication, p. 1042).

The compounds of the general formula (I) wherein  $R^6$  and  $R^7$  are hydrogen, may also be prepared by different procedures. The synthetic route depends on the last chemical transformation which has to be carried out.

In all cases in which the coupling of the tetrahydroisoquinoline with the amide side-chain is the final step the standard procedure shown in (Scheme 2) was followed. The tetrahydroisoquinolines as well as the amines ( $R^9R^{10}NH$ ) could be either commercially available or synthesized.



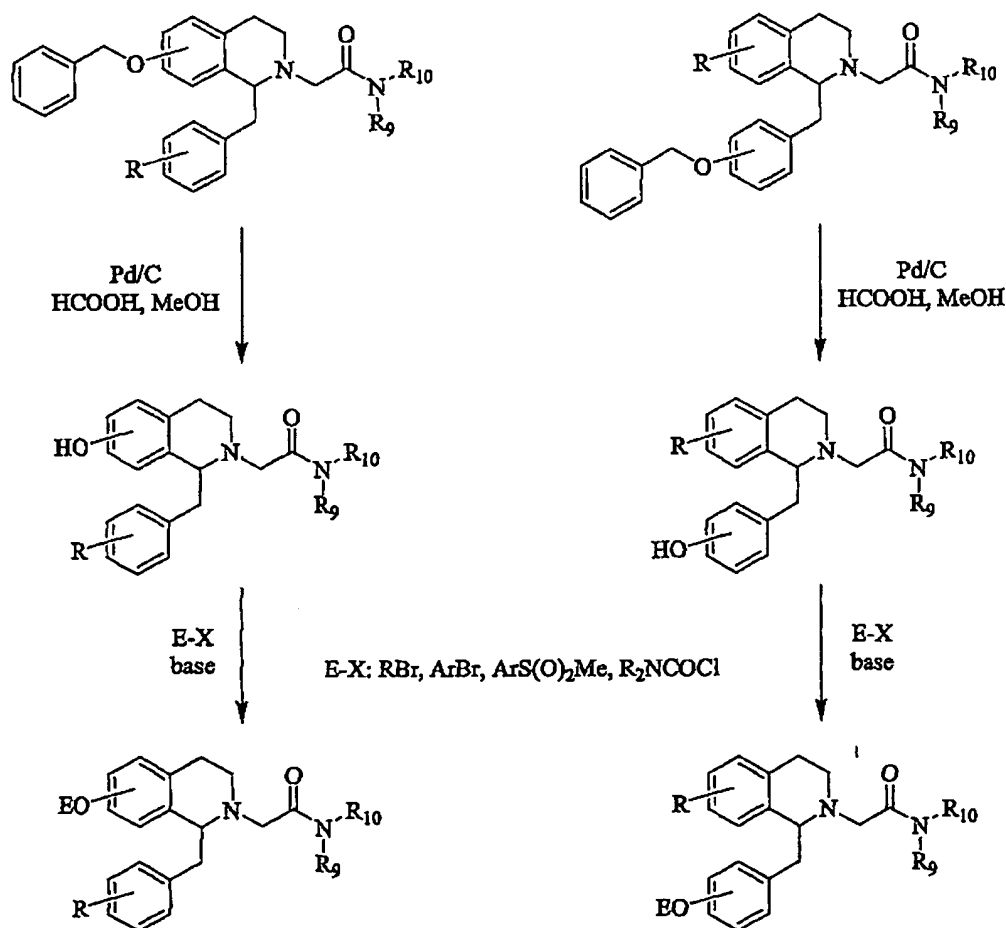
Scheme 2

Tetrahydroisoquinolines not commercially available might be prepared from the corresponding phenylethylamines by coupling with the desired carboxylic acid followed

by treatment with  $\text{POCl}_3$  and finally  $\text{NaBH}_4$  (see experimental part). All aminoindan-derivatives were prepared by reaction of 1-indanones with O-methylhydroxylamine followed by reduction with borane-tetrahydrofuran complex (Vaccaro W. *et al.*, *J. Med. Chem.*, 1996, 39, 1704-1719).

- 5 Compounds of general formula (I) wherein one substituent of the 1-benzyl-tetrahydroisoquinoline scaffold is a carbamoyloxy-, heteroaryloxy- or alkoxy-residue (not methoxy) are synthesized according to (Scheme 3). The benzyl-protected phenols are prepared by the procedure shown in (Scheme 2).

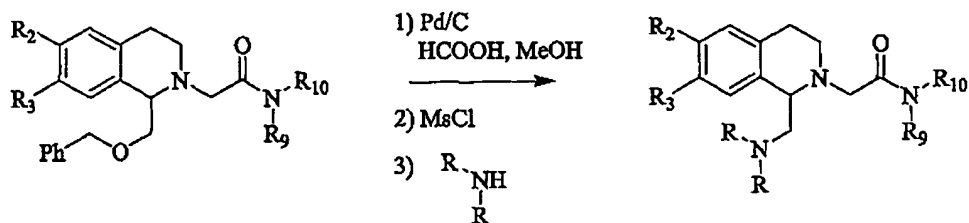
10



Scheme 3

- 15 In the case  $\text{R}^5$  (general formula I) is a heterocycl-methyl substituent the final step is the substitution of a mesylate function with the corresponding nitrogen containing nucleophile

according to (Scheme 4). The required starting material was synthesized by the same procedure as described earlier (Scheme 2).



5

Scheme 4

Stereochemically pure compounds of general formula I are obtained by kinetic resolution of the tetrahydroisoquinoline (Corrodi H., Hardegger E., *Helv. Chim. Acta*, 1956, 39, 889-897) and coupling of the pure enantiomer with the amide linker according to Scheme 2. Furthermore 2-[(1S)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-[(1S)-indan-1-yl]-acetamide could also be obtained by crystallization of the diastereoisomeric mixture of the two 2-{1[R,S]-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl}-N-[(1S)-indan-1-yl]-acetamides from methanol.

20

## Experimental Section

### I. Biology

#### Determination of OX<sub>1</sub> receptor antagonist activity

The OX<sub>1</sub> receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

#### Experimental method:

#### 30 Intracellular calcium measurements

Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor and the human orexin-2 receptor, respectively, were grown in culture medium (Ham F-12 with L-Glutamine) containing 300 µg/ml G418, 100 U/ml penicillin, 100 µg/ml streptomycin and 10 % inactivated foetal calf serum (FCS).

35

The cells were seeded at 80'000 cells / well into 96-well black clear bottom sterile plates (Costar) which had been precoated with 1% gelatine in Hanks' Balanced Salt Solution (HBSS). All reagents were from Gibco BRL.

The seeded plates were incubated overnight at 37°C in 5% CO<sub>2</sub>.

- 5 Human orexin-A as an agonist was prepared as 1 mM stock solution in methanol:water (1:1), diluted in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES for use in the assay at a final concentration of 10 nM.

Antagonists were prepared as 10 mM stock solution in DMSO, then diluted in 96-well plates, first in DMSO, then in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES.

10 On the day of the assay, 100 µl of loading medium (HBSS containing 1% FCS, 2 mM HEPES, 5 mM probenecid (Sigma) and 3 µM of the fluorescent calcium indicator fluo-3 AM (1 mM stock solution in DMSO with 10% pluronic acid) (Molecular Probes) was added to each well.

- 15 The 96-well plates were incubated for 60 min at 37° C in 5% CO<sub>2</sub>. The loading solution was then aspirated and cells were washed 3 times with 200 µl HBSS containing 2.5 mM probenecid, 0.1% BSA, 2 mM HEPES. 100 µl of that same buffer was left in each well. Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists were added to the plate in a volume of 50 µl, incubated for 20 min and finally 100 µl of
- 20 agonist was added. Fluorescence was measured for each well at 1 second intervals, and the height of each fluorescence peak was compared to the height of the fluorescence peak induced by 10 nM orexin-A with buffer in place of antagonist. For each antagonist, IC<sub>50</sub> value (the concentration of compound needed to inhibit 50 % of the agonistic response) was determined.

25

## II. Chemistry

30

The following examples illustrate the preparation of pharmacologically active compounds of the invention but do not at all limit the scope thereof. All temperatures are stated in °C.

All hydrochloride salts were prepared by dissolving the free-base in dichloromethane

and treating with an excess of ethereal HCl (2M).

#### General procedures:

5

##### A. General procedure A:

#### 1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-acetic acid benzyl ester

10

To a white suspension of 1-(4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-hydrochloride (1g, 2.632 mmol) in a mixture of toluene/ DMF (9/1) (10 ml), were added triethylamine (1.1 ml, 7.896 mmol) and chlorobenzylacetate (440  $\mu$ l, 2.895 mmol). The reaction mixture was stirred at reflux under argon for 20 h.

15  
After cooling, the mixture was diluted in CH<sub>2</sub>Cl<sub>2</sub> and washed with water.

The aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic phases were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated to give a crude brown- orange oil. Flash chromatography (AcOEt/ hexane 1/1) gave 1.15 g (89%) of the title product as a brown-orange oil.

20  
TLC (AcOEt/ hexane: 1/1): R<sub>f</sub> = 0.55.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 4.16 min. *m/z* = 492 (M + 1).

#### 1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-(3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid.

25

To a solution of 1-[(3,4-dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-acetic acid benzyl ester (1.15g, 2.34 mmol) in dry AcOEt (20 ml) was added in one portion Pd-C 10% (250mg). The resulting black suspension was hydrogenated at normal pressure and room temperature for 20 h. The mixture was then filtered over celite and concentrated in vacuo to give brown crystals.

30

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 3.34 min. *m/z* = 402 (M + 1).

#### Example 1

#### 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide

35

To a solution of 1-(4,5-dimethoxybenzyl)-6,7-dimethoxy-(3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid (100 mg, 0.249 mmol) in 4 ml of dry DMF, were added 129.6 mg (0.249 mmol) of PyBOP, 29.9  $\mu$ l (0.226 mmol) of benzylamine and dropwise 110  $\mu$ l (0.521 mmol) of diisopropylethylamine (Hünig's base). The mixture reaction was stirred at RT under argon for 20 h. The mixture was then dissolved in  $\text{CH}_2\text{Cl}_2$  and washed with water. The aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$ , the combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated to give a crude brown residue. Flash chromatography (AcOEt/ hexane 8/2) gave 126 mg (94%) of the title compound as a brown viscous oil.

TLC (AcOEt/ hexane: 8/2):  $R_f$  = 0.65.

LC-MS (MeCN/  $\text{H}_2\text{O}$ : 1/1):  $R_t$  = 4.83 min.  $m/z$  = 491 ( $M + 1$ ).

#### Example 2

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-naphthalen-1-ylmethyl-acetamide

In analogy to Example 1 but for the final step, reaction of 1-(4,5-dimethoxybenzyl)-6,7-dimethoxy-(3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid with 1-naphthalenemethylamine to give the title compound as the free-base (brown viscous oil) and the hydrochloride salt (brown crystals)

-TLC (AcOEt):  $R_f$  = 0.55.

-LC-MS (MeCN/ $\text{H}_2\text{O}$ : 1/1):  $R_t$  = 5.97 min.  $m/z$  = 541 ( $M + 1$ ).

#### Example 3

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(6-methoxy-naphthalen-2-ylmethyl)-acetamide

In analogy to Example 1 but for the final step, reaction of 1-(4,5-dimethoxybenzyl)-6,7-dimethoxy-(3,4-dihydro-1H-isoquinolin-2-yl)-acetic acid with 6-methoxynaphthalene-2-methylamine to give the title compound as the free-base (brown oil).



-TLC (AcOEt):  $R_f$  = 0.40 -LC-MS (MeCN/H<sub>2</sub>O: 1/1):  $R_t$  = 4.68 min.  $m/z$  = 571(M + 1).

**2-(3-Bromo-4-methoxy-phenyl)-N-[2-(3,4-dimethoxy)-ethyl]-acetamide**

LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  4.28 min, 409 (M+1, ES+).

5

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(3,4-dimethyl-phenyl)-acetamide**

LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  4.36 min, 328 (M+1, ES+).

**2-(3,4-Diethyl-phenyl)-N-[2-(3,4-dimethoxy)-ethyl]-acetamide**

10 LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  4.18 min, 356 (M+1, ES+).

**2-(3,4-Dichloro-phenyl)-N-[2-(3,4-dimethoxy)-ethyl]-acetamide**

LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  4.12 min, 369 (M+1, ES+).

15 **1-(4-Bromo-3-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline**

LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  2.96 min, 393 (M+1, ES+).

**1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline**

LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  3.19 min, 312 (M+1, ES+).

20

**1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline**

LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  2.25 min, 340 (M+1, ES+).

**1-(3,4-Dichloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline**

25 LC-MS (MeCN/ H<sub>2</sub>O: 1/1):  $R_t$  3.20 min, 353 (M+1, ES+).

**1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-phenyl- acetic acid methyl ester**

30 To a white suspension of 1-(4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-hydrochloride (5g, 0.013 mol) in dry toluene (50 ml), were added triethylamine (5.5 ml, 0.039 mol) and bromo-phenyl-acetic acid methyl ester (2.07 ml, 0.013 mol). The reaction mixture was stirred at reflux under argon for 20 h. After cooling,

the mixture was diluted in  $\text{CH}_2\text{Cl}_2$  and washed with water. The aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$ , the combined organic phases were dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated to give a crude brown- orange oil. Flash chromatography (AcOEt/ hexane 1/1) gave 5.85 g (90%) of the title product as a brown- orange oil.

TLC (AcOEt/ hexane: 1/1):  $R_f = 0.55$ .

LC-MS (MeCN/  $\text{H}_2\text{O}$ : 1/1):  $R_t$  4.00 min and  $R_t$  4.36 min, 492 (M+1, ES+).

**1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-phenyl- acetic acid**

To a solution of 1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-phenyl- acetic acid methyl ester (5.85 g, 0.011 mmol) in a mixture dioxane/ MeOH (4/3) (160 ml) was added dropwise 2M  $\text{NaOH}_{(\text{aq})}$  (81 ml). The resulting mixture was stirred at RT for 20 h under nitrogen. The mixture was then concentrated in vacuo, combined with water and AcOEt. The aqueous phase was acidified until pH 1 with 2N HCl, extracted three times with  $\text{CH}_2\text{Cl}_2$ , the combined organic phases were dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated to give the titled product (5.55 g, 97%) as yellow-green crystals.

LC-MS (MeCN/  $\text{H}_2\text{O}$ : 1/1):  $R_t$  3.62 min and  $R_t$  3.65 min, 478 (M+1, ES+).

**Example 4**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-N-indan-1-yl-2-phenyl-acetamide:**

To a solution of 1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-phenyl- acetic acid (100 mg, 0.209 mmol) in 5 ml of dry DMF, were added PyBOP (109 mg, 0.209 mmol) , 1-aminoindane (32.3 mg, 0.19 mmol) and dropwise diisopropylethylamine (Hünig's base). (75  $\mu\text{l}$ , 0.437 mmol). The mixture reaction was stirred at RT under argon for 20 h. The mixture was then dissolved in  $\text{CH}_2\text{Cl}_2$  and washed

with water. The aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$ , the combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated to give a crude brown residue. Flash chromatography (AcOEt) gave 72 mg (64%) of the title compound as a pale brown oil.

5 TLC (AcOEt):  $R_f = 0.65$ .

LC-MS (MeCN/  $\text{H}_2\text{O}$ : 1/1):  $R_t$  4.35 min and  $R_t$  4.60 min, 593 ( $M+1$ , ES+).

### Example 5

10

***N*-Butyl-2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-2-phenyl-acetamide**

prepared by reaction of 1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-phenyl- acetic acid with *n*-butylamine.

15 LC-MS (MeCN/  $\text{H}_2\text{O}$ : 1/1):  $R_t$  4.09 min 533 ( $M+1$ , ES+).

**1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-pyrimidin- acetic acid ethyl ester**

To a white suspension of 1-(4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-hydrochloride (1.65 g, 4.36 mmol) in dry DMF (5 ml), were added triethylamine (1.82 ml, 0.013 mol) and bromo-pyrimidin-acetic acid ethyl ester (1.07 g, 4.36 mmol). The reaction mixture was stirred at reflux under argon for 20 h. After cooling, the mixture was diluted in AcOEt and washed with water. The aqueous phase was extracted twice with  $\text{CH}_2\text{Cl}_2$ , the combined organic phases were dried over anhydrous AcOEt, filtered and concentrated to give a crude brown- orange oil. Flash chromatography (AcOEt) gave 1.4 g (63%) of the title product as a brown-orange oil.

25

TLC (AcOEt):  $R_f = 0.55$ .

LC-MS (MeCN/  $\text{H}_2\text{O}$ : 1/1):  $R_t$  4.54 min and  $R_t$  4.69 min, 508 ( $M+1$ , ES+).

30 **1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-pyrimidin- acetic acid**

To a solution of 1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-pyrimidin- acetic acid ethyl ester (1.4 g, 2.75 mmol) in a mixture dioxane/ MeOH

(4/3) (35 ml) was added dropwise 2M NaOH<sub>(aq)</sub> (24 ml). The resulting mixture was stirred at RT for 20 h under nitrogen. The mixture was then concentrated in vacuo, combined with water and AcOEt. The aqueous phase was acidified until pH 1 with 2N HCl, extracted three times with CH<sub>2</sub>Cl<sub>2</sub>, the combined organic phases were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated to give the titled product (1.23 g, 93%) as yellow-green crystals.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> 3.11 min and R<sub>t</sub> 3.24 min, 480 (M+1, ES+).

10

#### Example 6

15 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-2-*N*-indan-2-yl-2-pyrimidin-5-yl-acetamide

prepared by reaction of 1-[(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-naphthalen-2-yl]-pyrimidin- acetic acid with 2-aminoindane hydrochloride.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> 4.64 min and R<sub>t</sub> 4.83 min, 595 (M+1, ES+).

20

#### Example 7

*N*-benzyl-2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetamide:

25 prepared by reaction of 1-(3,4-dimethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 4.35 min, 459 (M+1, ES+).

#### Example 8

30

2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-indan-1-yl-acetamide:

prepared by reaction of 1-(3,4-dimethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-aminoindane.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 4.47 min, 485(M+1, ES+).

5 **Example 9**

**2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-pyridin-2-yl-acetamide:**

prepared by reaction of 1-(3,4-dimethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolylamine.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 2.99 min, 460 (M+1, ES+).

**Example 10**

15

**2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-pyridin-3-yl-acetamide:**

prepared by reaction of 1-(3,4-dimethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-picolylamine.

20 LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 2.61 min, 460 (M+1, ES+).

**Example 11**

**N-benzyl-2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-acetamide:**

25 prepared by reaction of 1-(3,4-diethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 4.35 min, 459 (M+1, ES+).

30 **Example 12**

**2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-diethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 2.87 min, 488 (M+1, ES+).

5 **Example 13**

**2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-3-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-diethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-picolyamine.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 2.85 min, 488 (M+1, ES+).

15 **Example 14**

**2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-4-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-diethyl-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-picolyamine.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 2.71 min, 488 (M+1, ES+).

**Example 15**

25 **2-[1-(3,4-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-dichloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine.

LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 3.72 min, 501 (M+1, ES+).

30

**Example 16**

2-[1-(3,4-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide:

prepared by reaction of 1-(3,4-dichloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-picolylamine.

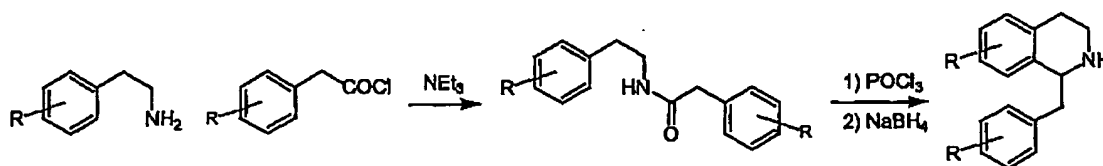
5 LC-MS (MeCN/ H<sub>2</sub>O: 1/1): R<sub>t</sub> = 3.29 min, 501 (M+1, ES<sup>+</sup>).

10

15

## B Coupling of 1,2,3,4-Tetrahydroisoquinolines with 2-Bromoacetamides

### B.1 Starting materials: Synthesis of 1,2,3,4-Tetrahydroisoquinoline derivatives:



20

#### B.1.1 Synthesis of the phenylethylamides:

##### Procedure I:

25

A solution of the respective phenylethylamine (80 mmol) and of triethylamine (90 mmol) in THF (120 mL) was cooled to 0°C and treated portionwise with the respective acetyl chloride (80 mmol). After stirring for 10 min at 0°C and for 14 h at room temperature a sat. aqueous NaHCO<sub>3</sub> solution was added, the phases were separated and the aqueous phase was extracted three times with ethyl acetate (150

mL). The solvent was removed in vacuo and the residue was either recrystallized from toluene or purified by flash chromatography to give the following amides:

**N-[2-(3-Methoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

6 prepared by reaction of 3-methoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS:  $t_r = 4.1$  min, 330 (M+1, ES+).

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-phenyl-acetamide:**

10 prepared by reaction of 3,4-dimethoxyphenylethylamine with phenyl acetyl chloride.

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-methoxyphenyl-acetamide:**

15 prepared by reaction of 3,4-dimethoxyphenylethylamine with 3-methoxyphenyl acetyl chloride.

LC-MS:  $t_r = 4.0$  min, 330 (M+1, ES+).

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-methoxyphenyl-acetamide:**

20 prepared by reaction of 3,4-dimethoxyphenylethylamine with 4-methoxyphenyl acetyl chloride.

LC-MS:  $t_r = 4.0$  min, 330 (M+1, ES+).

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2,5-dimethoxyphenyl-acetamide:**

25 prepared by reaction of 3,4-dimethoxyphenylethylamine with 2,5-dimethoxyphenyl acetyl chloride.

LC-MS:  $t_r = 4.1$  min, 360 (M+1, ES+).

**N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

30 prepared by reaction of 2,5-dimethoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS:  $t_r = 4.2$  min, 360 (M+1, ES+).



**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-phenyl-propionamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine with 3-phenyl propionyl chloride.

LC-MS: rt = 4.2 min, 314 (M+1, ES+).

5

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-phenyl-butyramide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine with 2-Phenylbutyryl chloride.

R<sub>f</sub> = 0.21 (ethyl acetate/heptane 1/1)

10

**N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-diphenyl-acetamide:**

prepared by reaction of 2,5-dimethoxyphenylethylamine with diphenylacetyl chloride.

LC-MS: rt = 5.3 min, 376 (M+1, ES+).

15

**N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-2,5-dimethoxyphenyl-acetamide:**

prepared by reaction of 2,5-dimethoxyphenylethylamine with 2,5-dimethoxyphenyl acetyl chloride.

LC-MS: rt = 4.6 min, 360 (M+1, ES+).

20

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-chlorophenyl-acetamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine with 4-chlorophenyl acetyl chloride.

LC-MS: rt = 4.4 min, 334 (M+1, ES+).

25

**N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-phenyl-acetamide:**

prepared by reaction of 2,5-dimethoxyphenylethylamine with phenylacetyl chloride.

LC-MS: rt = 4.5 min, 300 (M+1, ES+).

30

**N-[2-(3-methoxy-4-isopropoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

prepared by reaction of 3-methoxy-4-isopropoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS: rt = 4.2 min, 388 (M+1, ES+).

**N-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

prepared by reaction of 3,4,5-trimethoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS: rt = 3.8 min, 390 (M+1, ES+).

**N-[2-(2,3,4-Trimethoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

prepared by reaction of 2,3,4-trimethoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS: rt = 4.1 min, 390 (M+1, ES+).

**N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

prepared by reaction of 3,5-trimethoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS: rt = 4.2 min, 360 (M+1, ES+).

**N-[2-(3-Benzoyloxy-4-methoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

prepared by reaction of 3-benzoyloxy-4-methoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS: rt = 4.7 min, 436 (M+1, ES+), 434 (M-1, ES-).

**N-[2-(4-Benzoyloxy-3-methoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

prepared by reaction of 4-benzoyloxy-3-methoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS: rt = 4.8 min, 436 (M+1, ES+).

**N-[2-(2-Benzoyloxy-5-methoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

prepared by reaction of 2-benzoyloxy-5-methoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS: rt = 4.8 min, 436 (M+1, ES+).

**N-[2-(5-Benzoyloxy-2-methoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide:**

prepared by reaction of 5-benzyloxy-2-methoxyphenylethylamine with 3,4-dimethoxyphenyl acetyl chloride.

LC-MS:  $t_r = 4.9$  min, 436 (M+1, ES+).

5      **N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-benzyloxy-acetamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine with benzyloxy acetyl chloride.

LC-MS:  $t_r = 4.2$  min, 330 (M+1, ES+).

10

**Procedure II:**

A solution of the respective phenylethylamine (25.0 mmol) and the respective phenylacetic acid (25.0 mmol) in 100 mL toluene was refluxed for 24 h in the presence of a Dean-Stark. The solvent was removed in vacuo and the residue was  
15 either recrystallized from toluene or purified by flash chromatography to give the following amides:

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,4-methylenedioxyphenyl-acetamide:**

20 prepared by reaction of 3,4-dimethoxyphenylethylamine and 3,4-methylenedioxyphenylacetic acid.

LC-MS:  $t_r = 4.1$  min, 344 (M+1, ES+).

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-dimethylaminophenyl-acetamide:**

25 prepared by reaction of 3,4-dimethoxyphenylethylamine and 4-dimethylaminophenylacetic acid.

LC-MS:  $t_r = 3.1$  min, 343 (M+1, ES+).

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-fluorophenyl-acetamide:**

30 prepared by reaction of 3,4-dimethoxyphenylethylamine and 4-fluorophenyl-acetic acid.

LC-MS:  $t_r = 4.1$  min, 318 (M+1, ES+).

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,4-difluorophenyl-acetamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine and 3,4-difluorophenylacetic acid.

LC-MS:  $t_r = 4.2$  min, 336 (M+1, ES+).

5

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,4,5-trimethoxyphenyl-acetamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine and 3,4,5-trimethoxyphenylacetic acid.

LC-MS:  $t_r = 3.8$  min, 390 (M+1, ES+).

10

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2,3,4-trimethoxyphenyl-acetamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine and 2,3,4-trimethoxyphenylacetic acid.

LC-MS:  $t_r = 4.1$  min, 390 (M+1, ES+).

15

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-naphthalen-2-yl-acetamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine and 2-naphthylacetic acid.

LC-MS:  $t_r = 4.9$  min, 350 (M+1, ES+).

20

**N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-3,4-methylenedioxyphenyl-acetamide:**

prepared by reaction of 2,5-dimethoxyphenylethylamine and 3,4-methylenedioxyphenylacetic acid.

LC-MS:  $t_r = 4.3$  min, 344 (M+1, ES+).

25

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-hydroxy-3-methoxy-phenyl-acetamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine and 4-hydroxy-3-methoxy-phenylacetic acid.

LC-MS:  $t_r = 3.6$  min, 346 (M+1, ES+), 344 (M-1, ES-).

30

**N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-benzyloxy-4-methoxy-phenyl-acetamide:**

prepared by reaction of 3,4-dimethoxyphenylethylamine and 3-benzyloxy-4-methoxy-phenylacetic acid.

LC-MS:  $t_r = 4.6$  min, 436 (M+1, ES+), 434 (M-1, ES-).

**B.1.2. Synthesis of 1,2,3,4-Tetrahydroisoquinolines via Bischler-Napieralski-reaction (general procedure):**

5

To a suspension of the respective acetamide (60 mmol) in acetonitrile (100 mL) was added phosphorus oxychloride (16.2 mL, 177 mmol). The mixture was heated to reflux for 6 h and the solvent was removed in vacuo. The resulting oil was taken up in MeOH (70 mL), evaporated to dryness, dissolved in MeOH (130 mL) and cooled to 0°C. NaBH<sub>4</sub> was added in small (!) portions and the reaction mixture was stirred for 14 h. The solvent was removed in vacuo, dichloromethane (150 mL) and water (100 mL) were added, the phases were separated and the aqueous phase was extracted three times with dichloromethane (100 mL). The combined organic phases were concentrated in vacuo to give the following tetrahydroisoquinolines, which were purified either by flash chromatography or by crystallization as hydrochloride salt:

10

15

**1-(3,4-Dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline:**

20

prepared by cyclisation of N-[2-(3-Methoxy-phenyl)-ethyl]-3,4-dimethoxyphenyl-acetamide.

LC-MS:  $t_r = 3.1$  min, 314 (M+1, ES+).

**1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

25

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-phenyl acetamide.

R<sub>f</sub> (dichloromethane/methanol 5/1) = 0.51.

LC-MS:  $t_r = 3.1$  min, 284 (M+1, ES+).

**1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

30

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-methoxyphenyl acetamide.

LC-MS:  $t_r = 3.0$  min, 314 (M+1, ES+).

**1-(4-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-methoxyphenyl acetamide.

LC-MS: rt = 3.0 min, 314 (M+1, ES+).

5

**1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2,5-dimethoxy-phenyl acetamide.

LC-MS: rt = 3.2 min, 344 (M+1, ES+).

10

**1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

LC-MS: rt = 3.3 min, 344 (M+1, ES+).

15

**1-(2-Phenyl-ethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3-phenyl-propionamide.

20

LC-MS: rt = 3.2 min, 298 (M+1, ES+).

**1-(1-Phenyl-propyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-phenyl-butyramide.

25

LC-MS: rt = 3.3 min, 312 (M+1, ES+).

**1-(Diphenylmethyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-diphenyl acetamide.

30

LC-MS: rt = 3.7 min, 360 (M+1, ES+).

**1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-2,5-dimethoxy-phenyl acetamide.

LC-MS: rt = 3.6 min, 344 (M+1, ES+).

5      **1-(4-Chloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-chloro-phenyl acetamide.

LC-MS: rt = 3.2 min, 318 (M+1, ES+).

10      **1-Benzyl-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-phenyl acetamide.

LC-MS: rt = 3.4 min, 284 (M+1, ES+).

15

**1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydro-isoquinoline:**

20      prepared by cyclisation of N-[2-(3-Methoxy-4-isopropoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

LC-MS: rt = 3.32 min, 372 (M+1, ES+).

**1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

25      prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,4-methylenedioxy-phenyl acetamide.

LC-MS: rt = 3.0 min, 328 (M+1, ES+).

**1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

30      prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-dimethyl-amino-phenyl acetamide.

LC-MS: rt = 2.6 min, 327 (M+1, ES+).

**1-(4-Fluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-4-fluoro-phenyl acetamide.

LC-MS: rt = 3.1 min, 302 (M+1, ES+).

5

**1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,4-difluoro-phenyl acetamide.

LC-MS: rt = 3.1 min, 320 (M+1, ES+).

10

**1-(3,4,5-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-3,4,5-trimethoxy-phenyl acetamide.

LC-MS: rt = 3.0 min, 374 (M+1, ES+).

15

**1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3,4,5-Trimethoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

20

LC-MS: rt = 3.2 min, 374 (M+1, ES+).

**1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(2,3,4-Trimethoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

25

LC-MS: rt = 3.2 min, 374 (M+1, ES+).

**1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3,5-Dimethoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

30

LC-MS: rt = 3.5 min, 344 (M+1, ES+).



**1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2,3,4-trimethoxy-phenyl acetamide.

5 LC-MS: rt = 3.2 min, 374 (M+1, ES+).

**1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-naphthalen-2-yl acetamide.

10

LC-MS: rt = 3.6 min, 334 (M+1, ES+).

**1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(2,5-Dimethoxy-phenyl)-ethyl]-3,4-methylenedioxy-phenyl acetamide.

15

LC-MS: rt = 3.2 min, 328 (M+1, ES+).

**1-(3,4-Dimethoxy-benzyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3-Benzyloxy-4-methoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

20

LC-MS: rt = 3.7 min, 420 (M+1, ES+).

**1-(3,4-Dimethoxy-benzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(4-Benzyloxy-3-methoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

25

LC-MS: rt = 3.6 min, 420 (M+1, ES+).

30

**1-(3,4-Dimethoxy-benzyl)-5-benzyloxy-8-methoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(2-Benzyloxy-5-methoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

LC-MS: rt = 4.1 min, 420 (M+1, ES+).

5      **1-(3,4-Dimethoxy-benzyl)-8-benzyloxy-5-methoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(5-Benzyloxy-2-methoxy-phenyl)-ethyl]-3,4-dimethoxy-phenyl acetamide.

LC-MS: rt = 3.9 min, 420 (M+1, ES+).

10

**1-(4-Hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-4-hydroxy-3-methoxy-phenyl acetamide.

15

LC-MS: rt = 2.8 min, 330 (M+1, ES+).

20

**1-(3-Benzyloxy-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-3-benzyloxy-4-methoxy-phenyl acetamide.

LC-MS: rt = 3.6 min, 420 (M+1, ES+).

25

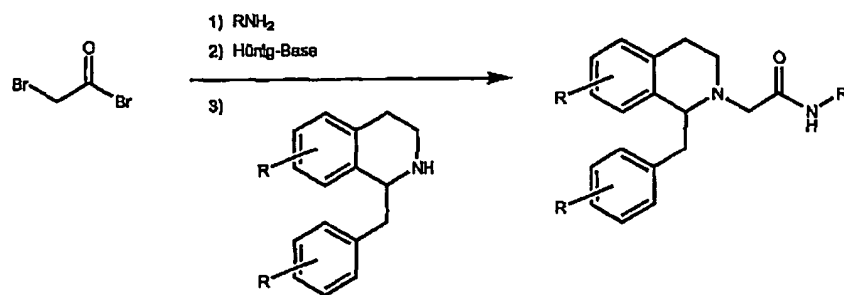
**1-Benzyloxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline:**

prepared by cyclisation of N-[2-(3,4-dimethoxy-phenyl)-ethyl]-benzyloxy-acetamide.

30

**B.2. Alkylation of 1,2,3,4-Tetrahydroisoquinolines with 2-Bromo-acetamides (general procedure)**

42



At  $-15^\circ\text{C}$  a solution of the respective amine in THF ( $250\ \mu\text{L}$ ,  $0.40\ \text{M}$ ) was added to a solution of 2-bromoacetyl bromide in THF ( $500\ \mu\text{L}$ ,  $0.20\ \text{M}$ ). The reaction mixture was treated with a solution of diisopropylethylamine in THF ( $250\ \mu\text{L}$ ,  $2.0\ \text{M}$ ), allowed to warm up to room temperature and stirred for 30 min. A solution of the respective tetrahydroisoquinoline in DMSO ( $500\ \mu\text{L}$ ,  $0.20\ \text{M}$ ) was added and the mixture was heated to  $75^\circ\text{C}$  for 18 h. After cooling to room temperature water ( $2.0\ \text{mL}$ ) and ethyl acetate ( $2.0\ \text{mL}$ ) were added, the phases were separated and the aqueous phase was extracted two times with ethyl acetate. The combined organic phases were concentrated in vacuo to give the following tetrahydroisoquinoline derivatives:

#### Example 17

**2-(1-Benzyl-3,4-dihydro-1H-isoquinolin-2-yl)-N-(2-methyl-benzyl)-acetamide:**  
 prepared by reaction of 1-Benzyl-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methylbenzylamine  
 LC-MS:  $\text{rt} = 4.6\ \text{min}$ ,  $385\ (\text{M}+1, \text{ES}^+)$ .

#### Example 18

**2-(1-Benzyl-3,4-dihydro-1H-isoquinolin-2-yl)-N-(2-chloro-benzyl)-acetamide:**  
 prepared by reaction of 1-Benzyl-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-chlorobenzylamine  
 LC-MS:  $\text{rt} = 4.7\ \text{min}$ ,  $405\ (\text{M}+1, \text{ES}^+)$ .

**Example 19**

**2-(1-Benzyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(1-naphthalen-1-yl-ethyl)-acetamide:**

prepared by reaction of 1-Benzyl-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-naphthaleneethylamine

LC-MS: *rt* = 4.7 and 4.8 min, 435 (*M*+1, ES+).

**Example 20**

**2-(1-Benzyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-benzyl-*N*-methyl-acetamide:**

prepared by reaction of 1-Benzyl-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *N*-benzylmethylamine

LC-MS: *rt* = 3.9 min, 385 (*M*+1, ES+).

**Example 21**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxybenzylamine

LC-MS: *rt* = 4.0 min, 491 (*M*+1, ES+).

**Example 22**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS: *rt* = 3.9 min, 461 (*M*+1, ES+).

**Example 23**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(4-methoxy-benzyl)-acetamide:

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-methoxybenzylamine  
LC-MS: *rt* = 3.9 min, 491 (M+1, ES+).

**Example 24**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(naphthalen-1-yl-methyl)-acetamide:

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-naphthalenemethylamine  
LC-MS: *rt* = 4.3 min, 511 (M+1, ES+).

**Example 25**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(3-methyl-benzyl)-acetamide:

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-methylbenzylamine  
LC-MS: *rt* = 4.1 min, 475 (M+1, ES+).

**Example 26**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(indan-1-yl)-acetamide:

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
LC-MS:  $t_r = 4.2$  min, 487 (M+1, ES+).

#### Example 27

5

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine  
10

LC-MS:  $t_r = 4.3$  min, 501 (M+1, ES+).

#### Example 28

15

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-piconylamine

LC-MS:  $t_r = 3.1$  min, 462 (M+1, ES+).

20

#### Example 29

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-4-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-piconylamine  
25

LC-MS:  $t_r = 3.1$  min, 462 (M+1, ES+).

**Example 30**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(2-fluoro-benzyl)-acetamide:

prepared by reaction of 1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-fluorobenzylamine

LC-MS: *rt* = 4.0 min, 479 (*M*+1, ES+).

**Example 31**

2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-benzyl-acetamide:

prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS: *rt* = 3.9 min, 431 (*M*+1, ES+).

**Example 32**

2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(indan-1-yl)-acetamide:

prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 1-amino-indane

LC-MS: *rt* = 4.2 min, 457 (*M*+1, ES+).

**Example 33**

2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:

prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine

LC-MS: *rt* = 4.3 min, 471 (*M*+1, *ES*<sup>+</sup>).

5

#### Example 34

**2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(pyridin-3-yl-methyl)-acetamide:**

10 prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-piconylamine

LC-MS: *rt* = 3.0 min, 432 (*M*+1, *ES*<sup>+</sup>).

#### Example 35

15

**2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(2-methyl-benzyl)-acetamide:**

prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methylbenzylamine

20 LC-MS: *rt* = 4.1 min, 445 (*M*+1, *ES*<sup>+</sup>).

#### Example 36

**2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(2,5-difluoro-benzyl)-acetamide:**

25

prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2,5-difluorobenzylamine

LC-MS: *rt* = 4.1 min, 467 (*M*+1, *ES*<sup>+</sup>).



**Example 37**

**2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(4-fluorobenzyl)-acetamide:**

5 prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-fluorobenzylamine

LC-MS: *rt* = 4.0 min, 449 (*M*+1, ES+).

**Example 38**

10

**2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(2-chlorobenzyl)-acetamide:**

prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-chlorobenzylamine

15

LC-MS: *rt* = 4.2 min, 465 (*M*+1, ES+).

**Example 39**

20

**2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(1-naphthalen-1-yl-ethyl)-acetamide:**

prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 1-naphthaleneethylamine

LC-MS: *rt* = 4.3 and 4.4 min, 495 (*M*+1, ES+).

25

**Example 40**

**2-(1-Benzyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-benzyl-*N*-methyl-acetamide:**

30 prepared by reaction of 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *N*-benzylmethylamine

LC-MS:  $rt = 3.8$  min, 445 (M+1, ES+).

**Example 41**

5      **2-[1-(3-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 2-methoxybenzylamine

LC-MS:  $rt = 4.0$  min, 491 (M+1, ES+).

10      **Example 42**

**2-[1-(3-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

15      prepared by reaction of 1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS:  $rt = 3.9$  min, 461 (M+1, ES+).

**Example 43**

20      **2-[1-(3-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(naphthalen-1-yl-methyl)-acetamide:**

prepared by reaction of 1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine

LC-MS:  $rt = 4.3$  min, 511 (M+1, ES+).

25      **Example 44**

**2-[1-(3-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(3-methyl-benzyl)-acetamide:**

prepared by reaction of 1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 3-methyl-benzylamine  
LC-MS:  $t_r = 4.1$  min, 475 (M+1, ES+).

5      **Example 45**

**2-[1-(3-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

10      prepared by reaction of 1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 1-Aminoindan  
LC-MS:  $t_r = 4.2$  min, 487 (M+1, ES+).

**Example 46**

15      **2-[1-(3-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:**

20      prepared by reaction of 1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine  
LC-MS:  $t_r = 4.3$  min, 501 (M+1, ES+).

**Example 47**

**2-[1-(3-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide:**

25      prepared by reaction of 1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 3-aminomethyl-pyridine  
LC-MS:  $t_r = 3.1$  min, 462 (M+1, ES+).

**Example 48**

**2-[1-(3-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-fluoro-benzyl)-acetamide:**

prepared by reaction of 1-(3-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 2-fluoro-benzylamine

5 LC-MS: rt = 4.0 min, 479 (M+1, ES+).

#### Example 49

10 **2-[1-(4-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 1-(4-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS: rt = 3.9 min, 461 (M+1, ES+).

15 **Example 50**

**2-[1-(4-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(naphthalen-1-yl-methyl)-acetamide:**

20 prepared by reaction of 1-(4-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine

LC-MS: rt = 4.2 min, 511 (M+1, ES+).

#### Example 51

25 **2-[1-(4-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide:**

prepared by reaction of 1-(4-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 1-Aminoindan

LC-MS: rt = 4.1 min, 487 (M+1, ES+).

**Example 52**

**2-[1-(4-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:**

5 prepared by reaction of 1-(4-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine  
LC-MS: *rt* = 4.2 min, 501 (M+1, ES+).

**Example 53**

10

**2-[1-(4-Methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-fluoro-benzyl)-acetamide:**

prepared by reaction of 1-(4-Methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 2-fluoro-benzylamine  
15 LC-MS: *rt* = 3.9 min, 479 (M+1, ES+).

**Example 54**

20

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxybenzylamine  
LC-MS: *rt* = 3.7 min, 521 (M+1, ES+).

25

**Example 55**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(4-methoxy-benzyl)-acetamide:**

30 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-methoxybenzylamine

LC-MS: rt = 3.7 min, 521 (M+1, ES+).

#### Example 56

5        **2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(3-methyl-benzyl)-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-methylbenzylamine  
LC-MS: rt = 3.8 min, 505 (M+1, ES+).

10

#### Example 57

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(indan-1-yl)-acetamide:  
15        prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
LC-MS: rt = 3.9 min, 517 (M+1, ES+).

20

#### Example 58

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(4-methyl-benzyl)-acetamide:  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
25        tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-methylbenzylamine  
LC-MS: rt = 3.8 min, 505 (M+1, ES+).

#### Example 59

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine

LC-MS: *rt* = 4.0 min, 531 (*M*+1, ES+).

**Example 60**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-piconylamine

LC-MS: *rt* = 2.9 min, 492 (*M*+1, ES+).

**Example 61**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-4-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-piconylamine

LC-MS: *rt* = 2.9 min, 492 (*M*+1, ES+).

**Example 62**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-phenyl-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with aniline

LC-MS: *rt* = 3.7 min, 477 (*M*+1, ES+).

**Example 63**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-fluoro-benzyl)-acetamide:**

5 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-fluorobenzylamine  
LC-MS: *rt* = 3.7 min, 509 (*M*+1, ES+).

**Example 64**

10 **2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[2-(4-methoxy-phenyl)-ethyl]-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-methoxyphenylethyl-  
15 amine  
LC-MS: *rt* = 3.8 min, 535 (*M*+1, ES+).

**Example 65**

20 **2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methyl-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methylbenzylamine  
LC-MS: *rt* = 3.9 min, 505 (*M*+1, ES+).

25

**Example 66**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-trifluoromethyl-benzyl)-acetamide:**

30 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-trifluorobenzylamine



LC-MS: *rt* = 4.0 min, 559 (M+1, ES+).

#### Example 67

5        2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
         *N*-(2,5-difluoro-benzyl)-acetamide:  
         prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
         tetrahydroisoquinoline and 2-bromoacetyl bromide with 2,5-difluorobenzylamine  
         LC-MS: *rt* = 3.8 min, 527 (M+1, ES+).

10

#### Example 68

         2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
         *N*-(4-fluoro-benzyl)-acetamide:  
15        prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
         tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-fluorobenzylamine  
         LC-MS: *rt* = 3.8 min, 509 (M+1, ES+).

#### Example 69

20        2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
         *N*-(2-chloro-benzyl)-acetamide:  
         prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
         tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-chlorobenzylamine  
25        LC-MS: *rt* = 3.9 min, 525 (M+1, ES+).

#### Example 70

         2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
30        *N*-(2,4-dimethoxy-benzyl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2,4-dimethoxybenzylamine

LC-MS: rt = 3.8 min, 551 (M+1, ES+).

5

#### Example 71

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1-phenyl-ethyl)-acetamide:

10 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-phenylethylamine

LC-MS: rt = 3.7 min, 505 (M+1, ES+).

#### Example 72

15

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1-naphthalen-1-yl-ethyl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-naphthaleneethylamine

20 LC-MS: rt = 4.0 min, 555 (M+1, ES+).

#### Example 73

25

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-*N*-methyl-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *N*-benzylmethylamine

LC-MS: rt = 3.6 min, 505 (M+1, ES+).

**Example 74**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-furan-2-yl-methyl-acetamide:**

5 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-aminomethylfuran  
LC-MS: rt = 3.5 min, 481 (M+1, ES+).

**Example 75**

10

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-but-2-yl-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-butylamine  
15 LC-MS: rt = 0.57 min, 457 (M+1, ES+).

**Example 76**

20

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine  
LC-MS: rt = 0.46 min, 492 (M+1, ES+).

25

**Example 77**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(4-methoxy-indan-1-yl)-acetamide:**

30 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-4-methoxy-indane

LC-MS: rt = 0.71 min, 547 (M+1, ES+).

#### Example 78

5        **2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(5,7-dimethyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
tetrahydroisoquinoline and 2-bromoacetyl bromide with 5,7-dimethyl-1,2,3,4-  
tetrahydro-1-naphthylamine  
10        LC-MS: rt = 0.80 min, 559 (M+1, ES+).

#### Example 79

15        **2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(2-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methyl-1,2,3,4-  
tetrahydro-1-naphthylamine  
LC-MS: rt = 0.76 min, 545 (M+1, ES+).

20

#### Example 80

25        **2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(6-methoxy-indan-1-yl)-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-  
tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-6-methoxy-  
indane  
LC-MS: rt = 0.72 min, 547 (M+1, ES+).

**Example 81**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-methyl-indan-1-yl)-acetamide:**

5 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-6-methyl-indane  
LC-MS: *rt* = 0.74 min, 531 (M+1, ES+).

**Example 82**

10

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(5-fluoro-indan-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-5-fluoro-indane  
15 LC-MS: *rt* = 0.72 min, 535 (M+1, ES+).

**Example 83**

20

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(5-methoxy-indan-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-5-methoxy-indane

LC-MS: *rt* = 0.75 min, 547 (M+1, ES+).

25

**Example 84**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(4-methyl-indan-1-yl)-acetamide:**

30 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-4-methyl-indane

LC-MS: rt = 0.86 min, 531 (M+1, ES+).

#### Example 85

5        **2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(3-methyl-indan-1-yl)-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-3-methyl-indane  
LC-MS: rt = 0.85 min, 531 (M+1, ES+).

10

#### Example 86

2-[(1*S*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide:  
15        prepared by reaction of (1*S*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*)-1-amino-indane  
LC-MS: rt = 3.8 min, 517 (M+1, ES+).

#### Example 87

20        **2-[(1*S*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*)-indan-1-yl]-acetamide:**  
prepared by reaction of (1*S*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*)-1-amino-indane  
25        LC-MS: rt = 3.9 min, 517 (M+1, ES+).

#### Example 88

2-[(1*S*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:  
30

prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine

LC-MS:  $rt = 4.0$  min, 531 (M+1, ES+).

5

#### Example 89

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

10 prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS:  $rt = 3.7$  min, 491 (M+1, ES+).

#### Example 90

15

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(naphthalen-1-yl-methyl)-acetamide:**

prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine

20

LC-MS:  $rt = 4.0$  min, 541 (M+1, ES+).

#### Example 91

25

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-methoxy-benzyl)-acetamide:**

prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzylamine

LC-MS:  $rt = 3.7$  min, 521 (M+1, ES+).

30

**Example 92**

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-ethoxy-benzyl)-acetamide:**

5 prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzylamine  
LC-MS: rt = 4.0 min, 535 (M+1, ES+).

**Example 93**

10

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-N-methyl-acetamide:**

prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with N-benzyl-N-methylamine  
15 LC-MS: rt = 3.7 min, 505 (M+1, ES+).

**Example 94**

20

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-[(1R,2S)-2-hydroxy-indan-1-yl]-acetamide:**

prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1R,2S)-1-amino-2-indanol

LC-MS: rt = 3.5 min, 533 (M+1, ES+).

25

**Example 95**

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-[(1S,2R)-2-hydroxy-indan-1-yl]-acetamide:**



prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1S,2R)-1-amino-2-indanol

LC-MS: rt = 3.5 min, 533 (M+1, ES+).

5

#### Example 96

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

10 prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolylamine

LC-MS: rt = 3.1 min, 492 (M+1, ES+).

#### Example 97

15

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-phenyl-ethyl)-acetamide:**

prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-phenyl-ethylamine

20 LC-MS: rt = 3.8 min, 505 (M+1, ES+).

#### Example 98

**2-[(1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(cyclohexyl-methyl)-acetamide:**

25

prepared by reaction of (1S)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with cyclohexyl-methylamine

LC-MS: rt = 4.0 min, 497 (M+1, ES+).

#### Example 99

30

**2-[1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(4-methoxy-benzyl)-acetamide:**

prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-methoxybenzylamine

5 LC-MS: *rt* = 3.9 min, 521 (*M*+1, ES+).

#### **Example 100**

**2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:**

10

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxybenzylamine

LC-MS: *rt* = 4.3 min, 521 (*M*+1, ES+).

15

#### **Example 101**

**2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

20

LC-MS: *rt* = 4.3 min, 491 (*M*+1, ES+).

#### **Example 102**

**2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide:**

25

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3,4-dimethoxyphenyl-ethylamine

30

LC-MS: *rt* = 4.3 min, 565 (*M*+1, ES+).

**Example 103**

**2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

5 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
LC-MS: *rt* = 4.5 min, 517 (M+1, ES+).

**Example 104**

10

**2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 3-picolylamine  
15 LC-MS: *rt* = 3.4 min, 492 (M+1, ES+).

**Example 105**

20

**2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-butyl-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *n*-butylamine  
LC-MS: *rt* = 4.2 min, 457 (M+1, ES+).

25

**Example 106**

**2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-fluoro-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-fluorobenzylamine  
30 LC-MS: *rt* = 4.4 min, 509 (M+1, ES+).

**Example 107**

2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
5 *N*-(pyridin-2-yl-methyl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine

LC-MS: *rt* = 3.7 min, 492 (M+1, ES+).

10 **Example 108**

2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-[1,3,4]thiadiazol-2-yl-acetamide:

15 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-amino-1,3,4-thiadiazole

LC-MS: *rt* = 3.8 min, 485 (M+1, ES+).

**Example 109**

20 2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(1*H*-benzimidazol-2-yl-methyl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-(aminomethyl)-benzimidazole

25 LC-MS: *rt* = 3.4 min, 531 (M+1, ES+).

**Example 110**

30 2-[1-(2-Phenyl-ethyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(pyridin-3-yl-methyl)-acetamide:

prepared by reaction of 1-(2-Phenyl-ethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 3-picolylamine  
LC-MS:  $t_r = 2.7$  min, 446 ( $M+1$ , ES+).

5      **Example 111**

**2-[1-(2-Phenyl-ethyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-fluoro-benzyl)-acetamide:**

10      prepared by reaction of 1-(2-Phenyl-ethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with 2-fluorobenzylamine  
LC-MS:  $t_r = 4.0$  min, 463 ( $M+1$ , ES+).

**Example 112**

15      **2-[1-(2-Phenyl-ethyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-cyclohexyl-acetamide:**

prepared by reaction of 1-(2-Phenyl-ethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with cyclohexylamine  
LC-MS:  $t_r = 4.0$  min, 437 ( $M+1$ , ES+).

20

**Example 113**

**2-[1-(1-Phenyl-propyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

25      prepared by reaction of 1-(1-Phenyl-propyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS:  $t_r = 4.4$  min, 459 ( $M+1$ , ES+).

**Example 114**

30

**2-[1-(1-Phenyl-propyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(1-Phenyl-propyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolylamine

5 LC-MS: *rt* = 3.7 min, 460 (*M*+1, ES+).

#### **Example 115**

**2-[1-(Diphenyl-methyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:**

10 prepared by reaction of 1-(Diphenyl-methyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzylamine

LC-MS: *rt* = 5.2 min, 537 (*M*+1, ES+).

#### **Example 116**

**2-[1-(Diphenyl-methyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(Diphenyl-methyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolylamine

20 LC-MS: *rt* = 4.3 min, 508 (*M*+1, ES+).

#### **Example 117**

**2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

25 prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane

LC-MS: *rt* = 4.6 min, 517 (*M*+1, ES+).

**Example 118**

**2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

5 prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS: *rt* = 4.4 min, 491 (*M*+1, ES+).

**Example 119**

10

**2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:**

prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzyl-amine  
15 LC-MS: *rt* = 4.5 min, 521 (*M*+1, ES+).

**Example 120**

20

**2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-ethoxy-benzyl)-acetamide:**

prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzyl-amine  
LC-MS: *rt* = 4.6 min, 535 (*M*+1, ES+).

25

**Example 121**

**2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:**

prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-indanol  
30

LC-MS:  $rt \approx 4.1$  min, 533 ( $M+1$ , ES $^{+}$ ).

#### Example 122

5      **2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-[(1*S*,2*R*)-2-hydroxy-indan-1-yl]-acetamide:**

prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-  
tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*,2*R*)-1-amino-2-  
indanol

10      LC-MS:  $rt \approx 4.1$  min, 533 ( $M+1$ , ES $^{+}$ ).

#### Example 123

15      **2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-  
tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolylamine

LC-MS:  $rt \approx 3.8$  min, 492 ( $M+1$ , ES $^{+}$ ).

#### 20      Example 124

**2-[1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(indan-2-yl)-acetamide:**

25      prepared by reaction of 1-(2,5-Dimethoxy-benzyl)-5,8-dimethoxy-1,2,3,4-  
tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-amino-indane

LC-MS:  $rt \approx 4.6$  min, 517 ( $M+1$ , ES $^{+}$ ).

#### Example 125



**2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 1-(4-Chloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane

5 LC-MS: *rt* = 4.8 min, 491 (*M*+1, ES+).

#### Example 126

**2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

10 prepared by reaction of 1-(4-Chloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS: *rt* = 4.4 min, 465 (*M*+1, ES+).

#### 15 Example 127

**2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-ethoxy-benzyl)-acetamide:**

20 prepared by reaction of 1-(4-Chloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzylamine

LC-MS: *rt* = 4.7 min, 509 (*M*+1, ES+).

#### Example 128

**2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:**

25 prepared by reaction of 1-(4-Chloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-indanol

LC-MS: *rt* = 4.0 min, 507 (*M*+1, ES+), 505 (*M*-1, ES-).

**Example 129**

**2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(4-Chloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine

LC-MS: rt = 3.6 min, 466 (M+1, ES+).

**Example 130**

**2-[1-(4-Chloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-2-yl)-acetamide:**

prepared by reaction of 1-(4-Chloro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-amino-indane

LC-MS: rt = 4.5 min, 491 (M+1, ES+).

**Example 131**

**2-(1-Benzyl-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-[(1*S*,2*R*)-2-hydroxy-indan-1-yl]-acetamide:**

prepared by reaction of 1-Benzyl-5,8-dimethoxy-1,2,3,4-tetrahydro-isoquinoline and 2-bromoacetyl bromide with (1*S*,2*R*)-1-amino-2-indanol

LC-MS: rt = 4.2 min, 473 (M+1, ES+).

**Example 132**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*)-1-amino-indane

LC-MS: *rt* = 4.1 min, 545 (M+1, ES+).

#### Example 133

5        **2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-  
1-naphthylamine  
10        LC-MS: *rt* = 4.3 min, 559 (M+1, ES+).

#### Example 134

15        **2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-benzyl-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS: *rt* = 3.9 min, 519 (M+1, ES+).

#### 20        Example 135

22        **2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(naphthalen-1-yl-methyl)-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
25        1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-  
methylamine  
LC-MS: *rt* = 4.3 min, 569 (M+1, ES+).

#### Example 136

30

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-methoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzylamine

LC-MS: rt = 4.0 min, 549 (M+1, ES+).

**Example 137**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-ethoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzylamine

LC-MS: rt = 4.2 min, 563 (M+1, ES+).

**Example 138**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-[(1R)-indan-1-yl]-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1R)-1-amino-indane

LC-MS: rt = 4.1 min, 545 (M+1, ES+).

**Example 139**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-N-methyl-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *N*-benzyl-*N*-methyl-amine

LC-MS: *rt* = 3.9 min, 533 (M+1, ES+).

5

#### Example 140

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:**

10

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine

LC-MS: *rt* = 4.0 min, 545 (M+1, ES+).

15

#### Example 141

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

20

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine

LC-MS: *rt* = 3.4 min, 520 (M+1, ES+).

#### Example 142

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*,2*R*)-2-hydroxy-indan-1-yl]-acetamide:**

25

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*,2*R*)-1-amino-2-indanol

LC-MS: *rt* = 3.8 min, 561 (M+1, ES+).

30

**Example 143**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-phenyl-ethyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-phenyl-ethylamine

LC-MS: rt = 4.0 min, 533 (M+1, ES+).

**Example 144**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-cyclohexyl-methyl-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with cyclohexyl-methylamine

LC-MS: rt = 4.2 min, 525 (M+1, ES+).

**Example 145**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(5,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 5,7-dimethyl-1,2,3,4-tetrahydro-1-naphthylamine

LC-MS: rt = 0.84 min, 587 (M+1, ES+).

**Example 146**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-  
isoquinolin-2-yl]-N-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methyl-1,2,3,4-  
5 tetrahydro-1-naphthylamine  
LC-MS: rt = 0.81 min, 573 (M+1, ES+).

#### Example 147

10 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-  
isoquinolin-2-yl]-N-(4-methyl-indan-1-yl)-acetamide:  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-4-  
methyl-indane  
15 LC-MS: rt = 0.79 min, 559 (M+1, ES+).

#### Example 148

20 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-  
isoquinolin-2-yl]-N-(4-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide:  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 4-methyl-1,2,3,4-  
tetrahydro-1-naphthylamine  
LC-MS: rt = 0.81 min, 573 (M+1, ES+).

#### Example 149

25 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-  
isoquinolin-2-yl]-N-(6-methoxy-indan-1-yl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-6-methoxy-indane

LC-MS: rt = 0.77 min, 575 (M+1, ES+).

5

#### Example 150

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(6-methyl-indan-1-yl)-acetamide:**

10 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-6-methyl-indane

LC-MS: rt = 0.80 min, 559 (M+1, ES+).

15

#### Example 151

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(5-fluoro-indan-1-yl)-acetamide:**

20 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-5-fluoro-indane

LC-MS: rt = 0.78 min, 563 (M+1, ES+).

#### Example 152

25

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-methyl-indan-1-yl)-acetamide:**

30 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-2-methyl-indane

LC-MS: rt = 0.79 min, 559 (M+1, ES+).



**Example 153**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(3-methyl-indan-1-yl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-3-  
methyl-indane

LC-MS: rt = 0.79 min, 559 (M+1, ES+).

**Example 154**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(3-phenyl-indan-1-yl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-3-phenyl-  
indane

LC-MS: rt = 0.86 min, 621 (M+1, ES+).

**Example 155**

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(5,6-dimethoxy-indan-1-yl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-  
1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-5,6-  
dimethoxy-indane

LC-MS: rt = 0.72 min, 605 (M+1, ES+).

**Example 156**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(5-methoxy-indan-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-5-methoxy-indane

LC-MS: rt = 0.76 min, 575 (M+1, ES+).

#### **Example 157**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(5-bromo-indan-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-5-bromo-indane

LC-MS: rt = 0.82 min, 623 (M+1, ES+).

#### **Example 158**

**2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-5-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ylamine

LC-MS: rt = 0.81 min, 573 (M+1, ES+).

#### **Example 159**

**2-[1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane

LC-MS: rt = 4.2 min, 501 (M+1, ES+).

**Example 160**

2-[1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:

prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS: *rt* = 4.0 min, 475 (*M*+1, ES+).

**Example 161**

2-[1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-ethoxy-benzyl)-acetamide:

prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzylamine

LC-MS: *rt* = 4.2 min, 519 (*M*+1, ES+).

**Example 162**

2-[1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:

prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-indanol

LC-MS: *rt* = 3.7 min, 517 (*M*+1, ES+), 515 (*M*-1, ES-).

**Example 163**

2-[1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-2-yl)-acetamide:

prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-amino-indane  
LC-MS: rt = 4.1 min, 501 (M+1, ES+).

5        **Example 164**

**2-[1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

10        prepared by reaction of 1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
LC-MS: rt = 3.7 min, 500 (M+1, ES+).

**Example 165**

15        **2-[1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**

20        prepared by reaction of 1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine  
LC-MS: rt = 3.9 min, 514 (M+1, ES+).

**Example 166**

25        **2-[1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

prepared by reaction of 1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS: rt = 3.5 min, 474 (M+1, ES+).

**Example 167**

**2-[1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(naphthalen-1-yl-methyl)-acetamide:**

5 prepared by reaction of 1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine

LC-MS: rt = 4.0 min, 524 (M+1, ES+).

10 **Example 168**

**2-[1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-methoxy-benzyl)-acetamide:**

15 prepared by reaction of 1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzylamine

LC-MS: rt = 3.6 min, 504 (M+1, ES+).

**Example 169**

20 **2-[1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-ethoxy-benzyl)-acetamide:**

prepared by reaction of 1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzylamine

LC-MS: rt = 3.8 min, 518 (M+1, ES+).

25

**Example 170**

**2-[1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-[(1R,2S)-2-hydroxy-indan-1-yl]-acetamide:**

prepared by reaction of 1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1R,2S)-1-amino-2-indanol

LC-MS: rt = 3.3 min, 516 (M+1, ES+).

5

#### Example 171

**2-[1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

10

prepared by reaction of 1-(4-Dimethylamino-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolylamine

LC-MS: rt = 2.9 min, 475 (M+1, ES+).

#### Example 172

15

**2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide:**

prepared by reaction of 1-(4-Fluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane

20

LC-MS: rt = 4.3 min, 475 (M+1, ES+).

#### Example 173

**2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**

25

prepared by reaction of 1-(4-Fluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine

LC-MS: rt = 4.5 min, 489 (M+1, ES+).

**Example 174**

**2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-ethoxy-benzyl)-acetamide:**

5 prepared by reaction of 1-(4-Fluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzylamine

LC-MS: rt = 4.3 min, 493 (M+1, ES+).

**Example 175**

10

**2-[1-(4-Fluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-*N*-methyl-acetamide:**

prepared by reaction of 1-(4-Fluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *N*-benzyl-*N*-methylamine

15 LC-MS: rt = 3.8 min, 463 (M+1, ES+).

**Example 176**

20

**2-[1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-*N*-methyl-acetamide:**

prepared by reaction of 1-(3,4-Difluoro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *N*-benzyl-*N*-methylamine

LC-MS: rt = 3.9 min, 481 (M+1, ES+).

25

**Example 177**

**2-[1-(3,4,5-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

30 prepared by reaction of 1-(3,4,5-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane

LC-MS: rt = 4.0 min, 547 (M+1, ES+).

**Example 178**

2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane

LC-MS: *rt* = 4.5 min, 547 (M+1, ES+).

**Example 179**

2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine

LC-MS: *rt* = 4.7 min, 561 (M+1, ES+).

**Example 180**

2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS: *rt* = 4.4 min, 521 (M+1, ES+).

**Example 181**

2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(naphthalen-1-yl-methyl)-acetamide:



prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine

LC-MS: rt = 4.8 min, 571 (M+1, ES+).

5

#### Example 182

**2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-methoxy-benzyl)-acetamide:**

10

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzyl-amine

LC-MS: rt = 4.4 min, 551 (M+1, ES+).

#### Example 183

15

**2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-ethoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzyl-amine

20

LC-MS: rt = 4.6 min, 565 (M+1, ES+).

#### Example 184

**2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-N-methyl-acetamide:**

25

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with N-benzyl-N-methylamine

LC-MS: rt = 4.0 min, 535 (M+1, ES+).

**Example 185**

2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*,2*R*)-2-hydroxy-indan-1-yl]-acetamide:

5 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*,2*R*)-1-amino-2-indanol

LC-MS: *rt* = 4.0 min, 563 (*M*+1, *ES*+), 561 (*M*-1, *ES*-).

10 **Example 186**

2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:

15 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-indanol

LC-MS: *rt* = 4.0 min, 563 (*M*+1, *ES*+).

20 **Example 187**

2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

25 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolylamine

LC-MS: *rt* = 3.7 min, 522 (*M*+1, *ES*+).

**Example 188**

30 2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-phenyl-ethyl)-acetamide:

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-phenyl-ethylamine  
LC-MS: rt = 4.5 min, 535 (M+1, ES+).

5      **Example 189**

**2-[1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(cyclohexyl-methyl)-acetamide:**

10      prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with cyclohexyl-methylamine  
LC-MS: rt = 4.6 min, 527 (M+1, ES+).

**Example 190**

15      **2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
LC-MS: rt = 4.3 min, 547 (M+1, ES+).

20

**Example 191**

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**

25      prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine  
LC-MS: rt = 4.4 min, 561 (M+1, ES+).

**Example 192**

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

5 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS: rt = 4.1 min, 521 (M+1, ES+).

**Example 193**

10

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(naphthalen-1-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine  
15 LC-MS: rt = 4.5 min, 571 (M+1, ES+).

**Example 194**

20

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-methoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzyl-amine  
LC-MS: rt = 4.2 min, 551 (M+1, ES+).

25

**Example 195**

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(2-ethoxy-benzyl)-acetamide:**

30 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzyl-amine

LC-MS: rt = 4.3 min, 565 (M+1, ES+).

#### Example 196

5        **2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-*N*-methyl-acetamide:**  
prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *N*-benzyl-*N*-methyl-amine  
LC-MS: rt = 3.9 min, 535 (M+1, ES+).

10

#### Example 197

2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:  
15        prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-indanol  
LC-MS: rt = 3.8 min, 563 (M+1, ES+), 561 (M-1, ES-).

20

#### Example 198

2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*,2*R*)-2-hydroxy-indan-1-yl]-acetamide:  
25        prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*,2*R*)-1-amino-2-indanol  
LC-MS: rt = 3.8 min, 563 (M+1, ES+), 561 (M-1, ES-).

#### Example 199

30

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine

5 LC-MS: *rt* = 3.4 min, 522 (*M*+1, ES+).

#### **Example 200**

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-phenyl-ethyl)-acetamide:**

10 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-phenyl-ethylamine

LC-MS: *rt* = 4.2 min, 535 (*M*+1, ES+).

#### **Example 201**

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(cyclohexyl-methyl)-acetamide:**

20 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with cyclohexyl-methylamine

LC-MS: *rt* = 4.3 min, 527 (*M*+1, ES+).

#### **Example 202**

**2-[1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-2-yl)-acetamide:**

25 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-amino-indane

LC-MS: *rt* = 4.2 min, 547 (*M*+1, ES+).

**Example 203**

**2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide:**

5 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*)-1-amino-indane  
LC-MS: rt = 4.4 min, 517 (M+1, ES+).

**Example 204**

10

**2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*)-indan-1-yl]-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*)-1-amino-indane  
15 LC-MS: rt = 4.4 min, 517 (M+1, ES+).

**Example 205**

20

**2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine  
LC-MS: rt = 4.5 min, 531 (M+1, ES+).

25

**Example 206**

**2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

30 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS: rt = 4.2 min, 491 (M+1, ES+).

#### Example 207

5        **2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(naphthalen-1-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine

10        LC-MS: rt = 4.5 min, 541 (M+1, ES+).

#### Example 208

15        **2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(2-methoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzyl-amine

LC-MS: rt = 4.2 min, 521 (M+1, ES+).

#### 20        Example 209

**2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
N-(2-ethoxy-benzyl)-acetamide:**

25        prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzyl-amine

LC-MS: rt = 4.4 min, 535 (M+1, ES+).

#### Example 210



**2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine

5 LC-MS: *rt* = 4.2 min, 492 (*M*+1, ES+).

#### **Example 211**

**2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:**

10 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-indanol

LC-MS: *rt* = 3.9 min, 533 (*M*+1, ES+).

15

#### **Example 212**

**2-[1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*,2*R*)-2-hydroxy-indan-1-yl]-acetamide:**

20 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*,2*R*)-1-amino-2-indanol

LC-MS: *rt* = 3.9 min, 533 (*M*+1, ES+).

25

#### **Example 213**

**2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

30 prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane

LC-MS: *rt* = 4.1 min, 547 (*M*+1, ES+).

**Example 214**

2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:

prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine

LC-MS:  $t_r = 4.3$  min, 561 ( $M+1$ , ES+).

**Example 215**

2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:

prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS:  $t_r = 3.9$  min, 521 ( $M+1$ , ES+).

**Example 216**

2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(naphthalen-1-yl-methyl)-acetamide:

prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine

LC-MS:  $t_r = 4.3$  min, 571 ( $M+1$ , ES+).

**Example 217**

2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:

prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzyl-amine  
LC-MS: *rt* = 4.0 min, 551 (*M*+1, *ES*+).

#### Example 218

2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-ethoxy-benzyl)-acetamide:

prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzyl-amine  
LC-MS: *rt* = 4.1 min, 565 (*M*+1, *ES*+).

#### Example 219

2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:

prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-indanol  
LC-MS: *rt* = 3.7 min, 563 (*M*+1, *ES*+), 561 (*M*-1, *ES*-).

#### Example 220

2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-phenyl-ethyl)-acetamide:

prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-phenyl-ethylamine  
LC-MS: *rt* = 4.0 min, 535 (*M*+1, *ES*+).

**Example 221**

**2-[1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-2-yl)-acetamide:**

5 prepared by reaction of 1-(2,3,4-Trimethoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-amino-indane  
LC-MS: rt = 4.1 min, 547 (M+1, ES+).

**Example 222**

10

**2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
15 LC-MS: rt = 4.8 min, 507 (M+1, ES+).

**Example 223**

**2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:**

20 prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine  
LC-MS: rt = 4.9 min, 521 (M+1, ES+).

25

**Example 224**

**2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

30 prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine

LC-MS: rt = 4.5 min, 481 (M+1, ES+).

#### Example 225

- 5        **2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(naphthalen-1-yl-methyl)-acetamide:**  
prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine  
10        LC-MS: rt = 4.8 min, 531 (M+1, ES+).

#### Example 226

- 15        **2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:**  
prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzyl-amine  
LC-MS: rt = 4.5 min, 511 (M+1, ES+).

#### 20        Example 227

- 25        **2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-ethoxy-benzyl)-acetamide:**  
prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzyl-amine  
LC-MS: rt = 4.7 min, 525 (M+1, ES+).

#### Example 228

**2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-*N*-methyl-acetamide:**

prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with *N*-benzyl-*N*-methyl-amine  
LC-MS: *rt* = 4.2 min, 495 (*M*+1, *ES*+).

#### Example 229

**1-(3,4-Dihydro-1*H*-isoquinolin-2-yl)-2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanone:**

prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydroisoquinoline  
LC-MS: *rt* = 4.3 min, 507 (*M*+1, *ES*+).

#### Example 230

**2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolylamine  
LC-MS: *rt* = 4.4 min, 482 (*M*+1, *ES*+).

#### Example 231

**2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:**

prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-indanol  
LC-MS: *rt* = 4.1 min, 523 (*M*+1, *ES*+), 521 (*M*-1, *ES*-).

**Example 232**

2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*,2*R*)-2-hydroxy-indan-1-yl]-acetamide:

5 prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*S*,2*R*)-1-amino-2-indanol

LC-MS: *rt* = 4.1 min, 523 (*M*+1, *ES*+), 521 (*M*-1, *ES*-).

10 **Example 233**

2-[1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-2-yl)-acetamide:

15 prepared by reaction of 1-(Naphthalen-2-yl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-amino-indane

LC-MS: *rt* = 4.7 min, 507 (*M*+1, *ES*+).

**Example 234**

20 2-[1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide:

prepared by reaction of 1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1,2,3,4-tetrahydro-1-naphthylamine

25 LC-MS: *rt* = 4.7 min, 579 (*M*+1, *ES*+).

**Example 235**

30 2-[1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

prepared by reaction of 1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
LC-MS: rt = 4.5 min, 565 (M+1, ES+).

5        **Example 236**

**2-[1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

10        prepared by reaction of 1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS: rt = 4.3 min, 539 (M+1, ES+).

**Example 237**

15        **2-[1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(naphthalen-1-yl-methyl)-acetamide:**

prepared by reaction of 1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with naphthalen-1-yl-methylamine  
20        LC-MS: rt = 4.7 min, 589 (M+1, ES+).

**Example 238**

25        **2-[1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-ethoxy-benzyl)-acetamide:**

prepared by reaction of 1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-ethoxy-benzylamine  
LC-MS: rt = 4.6 min, 583 (M+1, ES+).



**Example 239**

**2-[1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

5 prepared by reaction of 1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine  
LC-MS: *rt* = 3.6 min, 541 (*M*+1, ES+).

**Example 240**

10

**2-[1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*R*,2*S*)-2-hydroxy-indan-1-yl]-acetamide:**

prepared by reaction of 1-(3-Bromo-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with (1*R*,2*S*)-1-amino-2-  
15 indanol  
LC-MS: *rt* = 4.0 min, 581 (*M*+1, ES+), 579 (*M*-1, ES-).

**Example 241**

20

**2-[1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine  
LC-MS: *rt* = 3.8 min, 476 (*M*+1, ES+).

25

**Example 242**

**2-[1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methoxy-benzyl)-acetamide:**

30 prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-methoxy-benzylamine

LC-MS: rt = 4.6 min, 505 (M+1, ES+).

#### Example 243

5        **2-[1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[1,3,4]thiadiazol-2-yl-acetamide:**  
prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-amino-1,3,4-thiadiazole  
LC-MS: rt = 4.4 min, 469 (M+1, ES+).

10

#### Example 244

2-[1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1*H*-benzoimidazol-2-yl-methyl)-acetamide:  
15        prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-(aminomethyl)-benzimidazole  
LC-MS: rt = 3.8 min, 515 (M+1, ES+).

#### 20        Example 245

2-[1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1*H*-indazol-6-yl)-acetamide:  
prepared by reaction of 1-(3,4-Methylenedioxy-benzyl)-5,8-dimethoxy-1,2,3,4-  
25        tetrahydroisoquinoline and 2-bromoacetyl bromide with 6-aminoindazole  
LC-MS: rt = 4.4 min, 501 (M+1, ES+).

30        Analogous to the above mentioned procedure, but in larger scale, the following tetrahydroisoquinoline derivatives were synthesized:

**Example 246**

**2-[1-(3,4-Dimethoxy-benzyl)-6-benzyloxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

5 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS: rt = 4.5 min, 567 (M+1, ES+).

**Example 247**

10

**2-[1-(3,4-Dimethoxy-benzyl)-7-benzyloxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
15 LC-MS: rt = 4.4 min, 567 (M+1, ES+).

**2-[1-(3,4-Dimethoxy-benzyl)-7-benzyloxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide:**

20 prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
LC-MS: rt = 4.5 min, 593 (M+1, ES+).

**Example 248**

25

**2-[1-(3,4-Dimethoxy-benzyl)-5-benzyloxy-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-5-benzyloxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine  
30 LC-MS: rt = 4.4 min, 568 (M+1, ES+).

**2-[1-(3,4-Dimethoxy-benzyl)-8-benzyloxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 1-(3,4-Dimethoxy-benzyl)-8-benzyloxy-5-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 2-picolyamine  
LC-MS: rt = 4.4 min, 568 (M+1, ES+).

**Example 249**

**2-[1-(4-Hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 1-(4-Hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS: rt = 3.4 min, 477 (M+1, ES+).

**2-[1-(3-Benzyloxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 1-(3-Benzyloxy-4-methoxy-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with benzylamine  
LC-MS: rt = 4.4 min, 567 (M+1, ES+).

**2-(1-Benzyloxymethyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-(indan-1-yl)-acetamide:**

prepared by reaction of 1-Benzyloxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline and 2-bromoacetyl bromide with 1-amino-indane  
LC-MS: rt = 4.3 min, 487 (M+1, ES+).

**C Coupling of Phenols with Alkylbromides, Heteroarylchlorides, Heteroaryl-methyl-sulfones and Carbamoylchlorides**

**C.1 Starting materials: Deprotection of Benzylic ethers:**

To a mixture of MeOH (60 mL) and formic acid (11.0 mL) was added Palladium (10% Pd/C, wet, 274 mg). The respective benzylic ether (4.0 mmol) was added portionwise and the mixture was stirred for 40 h. During this period further portions of Pd/C were added until the starting material was consumed. The mixture was filtered, the solvent was removed in vacuo and the residue was purified by flash-chromatography to give the following phenols:

#### Example 250

**2-[1-(3,4-dimethoxy-benzyl)-6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by deprotection of 2-[1-(3,4-dimethoxy-benzyl)-6-benzyloxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide

LC-MS: rt = 3.5 min, 477 (M+1, ES+).

#### Example 251

**2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by deprotection of 2-[1-(3,4-dimethoxy-benzyl)-7-benzyloxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide

LC-MS: rt = 3.5 min, 477 (M+1, ES+).

#### Example 252

**2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide:**

prepared by deprotection of 2-[1-(3,4-dimethoxy-benzyl)-7-benzyloxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide

LC-MS: rt = 3.7 min, 503 (M+1, ES+), 501 (M-1, ES-).

**2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

5 prepared by deprotection of 2-[1-(3,4-dimethoxy-benzyl)-5-benzyloxy-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide  
LC-MS: rt = 3.2 min, 478 (M+1, ES+), 476 (M-1, ES-).

10 **2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

prepared by deprotection of 2-[1-(3,4-dimethoxy-benzyl)-8-benzyloxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide  
LC-MS: rt = 3.3 min, 478 (M+1, ES+), 476 (M-1, ES-).

15 **Example 253**

**2-[1-(3-Hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

20 prepared by deprotection of 2-[1-(3-Benzyloxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:  
LC-MS: rt = 3.5 min, 477 (M+1, ES+), 475 (M-1, ES-).

25 **2-(1-Hydroxymethyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-(indan-1-yl)-acetamide:**

prepared by deprotection of 2-(1-Benzyloxymethyl-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-(indan-1-yl)-acetamide:  
LC-MS: rt = 3.1 min, 397 (M+1, ES+).

30

**C.2 Alkylation of Phenols with Alkylbromides (general procedure):**

At RT a solution of the respective phenol in DMF (250  $\mu$ L, 0.40 M) was added to  $K_2CO_3$  (70 mg). The reaction mixture was treated with a solution of the respective alkyl bromide in DMF (150  $\mu$ L, 1.00 M), shaken at 100°C for 90 min and cooled to RT. After addition of another portion of alkyl bromide (150  $\mu$ L, 1.00 M), shaking (100°C, 90 min) and cooling to RT a solution of triethylamine in THF (250  $\mu$ L, 2.0 M) was added and the mixture was shaken for 14 h. Water (2.0 mL) and ethyl acetate (2.0 mL) were added, the phases were separated and the aqueous phase was extracted two times with ethyl acetate. The combined organic phases were concentrated in vacuo to give the following tetrahydroisoquinoline derivatives:

#### Example 254

**2-[1-(3,4-dimethoxy-benzyl)-6-ethoxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with ethyl iodide

LC-MS:  $t_r$  = 3.8 min, 505 (M+1, ES+).

#### Example 255

**2-[1-(3,4-dimethoxy-benzyl)-6-propoxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with propyl bromide

LC-MS:  $t_r$  = 4.1 min, 519 (M+1, ES+).

#### Example 256

**2-[1-(3,4-dimethoxy-benzyl)-6-allyloxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with allyl bromide

LC-MS:  $t_r = 4.0$  min, 517 (M+1, ES+).

**Example 257**

**2-[1-(3,4-dimethoxy-benzyl)-6-(cyclopropyl-methoxy)-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with cyclopropylmethyl bromide

LC-MS:  $t_r = 4.1$  min, 531 (M+1, ES+).

**Example 258**

**[2-(Benzylcarbamoyl-methyl)-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,2,3,4-tetrahydro-isoquinolin-6-yloxy]-acetic acid ethyl ester:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with ethyl bromoacetate

**Example 259**

**2-[1-(3,4-dimethoxy-benzyl)-6-(3-fluoro-propoxy)-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-6-hydroxy-7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with 1-bromo-3-fluoro-propane



LC-MS: rt = 4.0 min, 537 (M+1, ES+).

#### Example 260

5        **2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**  
prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with ethyl iodide  
LC-MS: rt = 3.8 min, 505 (M+1, ES+).

10

#### Example 261

15        **2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**  
prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with propyl bromide  
LC-MS: rt = 4.0 min, 519 (M+1, ES+).

20

#### Example 262

25        **2-[1-(3,4-dimethoxy-benzyl)-7-butoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**  
prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with butyl bromide  
LC-MS: rt = 4.2 min, 533 (M+1, ES+).

30

#### Example 263

**2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with allyl bromide

LC-MS: rt = 3.9 min, 517 (M+1, ES+).

#### **Example 264**

**2-[1-(3,4-dimethoxy-benzyl)-7-(cyclopropyl-methoxy)-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with cyclopropylmethyl bromide

LC-MS: rt = 4.0 min, 531 (M+1, ES+).

#### **Example 265**

**[2-(Benzylcarbamoyl-methyl)-1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-acetic acid ethyl ester:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with ethyl bromoacetate

LC-MS: rt = 4.0 min.

#### **Example 266**

**2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with ethyl iodide  
LC-MS: *rt* = 0.73 min, 531 (*M*+1, *ES*+).

5        **Example 267**

**2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

10        prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with propyl bromide  
LC-MS: *rt* = 0.77 min, 545 (*M*+1, *ES*+).

15        **Example 268**

**2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

20        prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with allyl bromide  
LC-MS: *rt* = 0.75 min, 543 (*M*+1, *ES*+).

**Example 269**

25        **2-[1-(3,4-dimethoxy-benzyl)-7-isopropoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with isopropyl bromide  
LC-MS: *rt* = 0.75 min, 545 (*M*+1, *ES*+).

**Example 270**

**2-[1-(3,4-dimethoxy-benzyl)-7-butoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

5 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with butyl bromide  
LC-MS: *rt* = 0.81 min, 559 (*M*+1, ES+).

**Example 271**

10

**2-[1-(3,4-dimethoxy-benzyl)-7-isobutoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 1-bromo-2-methyl-  
15 propane  
LC-MS: *rt* = 0.80 min, 559 (*M*+1, ES+).

**Example 272**

20

**2-[1-(3,4-dimethoxy-benzyl)-7-(but-2-oxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-bromo-butane  
LC-MS: *rt* = 0.78 min, 559 (*M*+1, ES+).

25

**Example 273**

**2-[1-(3,4-dimethoxy-benzyl)-7-(cyclopropyl-methoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with cyclopropyl-methyl bromide

LC-MS: *rt* = 0.76 min, 557 (M+1, ES+).

5

#### Example 274

**2-[1-(3,4-dimethoxy-benzyl)-7-cyclohexyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

10 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with cyclohexyl bromide

LC-MS: *rt* = 0.82 min, 585 (M+1, ES+).

#### Example 275

15 **[2-(Indan-1-ylcarbamoyl-methyl)-1-(3,4-dimethoxy-benzyl)-6-methoxy-1,2,3,4-tetrahydro-isoquinolin-7-yloxy]-acetic acid methyl ester:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with methyl bromoacetate

LC-MS: *rt* = 0.70 min, 575 (M+1, ES+).

20

#### Example 276

**2-[1-(3,4-dimethoxy-benzyl)-7-(3-fluoro-propoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

25 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 1-bromo-3-fluoro-propane

LC-MS: *rt* = 0.74 min, 563 (M+1, ES+).

**Example 277**

2-[1-(3,4-dimethoxy-benzyl)-7-(2-fluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

5 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 1-bromo-2-fluoro-ethane

LC-MS: *rt* = 0.72 min, 549 (*M*+1, ES+).

10 **Example 278**

2-[1-(3,4-dimethoxy-benzyl)-7-(2,2-difluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

15 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 1-bromo-2,2-difluoro-ethane

LC-MS: *rt* = 0.75 min, 567 (*M*+1, ES+).

20 **Example 279**

2-[1-(3,4-dimethoxy-benzyl)-5-ethoxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

25 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with ethyl iodide

LC-MS: *rt* = 0.61 min, 506 (*M*+1, ES+).

**Example 280**

30 2-[1-(3,4-dimethoxy-benzyl)-5-propoxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with propyl bromide

LC-MS: *rt* = 0.66 min, 520 (*M*+1, ES+).

5

#### Example 281

**2-[1-(3,4-dimethoxy-benzyl)-5-allyloxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

10 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with allyl bromide

LC-MS: *rt* = 0.63 min, 518 (*M*+1, ES+).

#### Example 282

15

**2-[1-(3,4-dimethoxy-benzyl)-5-isopropoxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

20 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with isopropyl bromide

LC-MS: *rt* = 0.64 min, 520 (*M*+1, ES+).

#### Example 283

25

**2-[1-(3,4-dimethoxy-benzyl)-5-butoxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

26 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with butyl bromide

30 LC-MS: *rt* = 0.70 min, 534 (*M*+1, ES+).

**Example 284**

**2-[1-(3,4-dimethoxy-benzyl)-5-isobutoxy-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

5 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide with 1-bromo-2-methyl-propane

LC-MS:  $rt = 0.70$  min, 534 (M+1, ES+).

10 **Example 285**

**2-[1-(3,4-dimethoxy-benzyl)-5-(but-2-oxy)-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

15 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide with 2-bromo-butane

LC-MS:  $rt = 0.68$  min, 534 (M+1, ES+).

20 **Example 286**

**2-[1-(3,4-dimethoxy-benzyl)-5-(cyclopropyl-methoxy)-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

25 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide with cyclopropyl-methyl bromide

LC-MS:  $rt = 0.66$  min, 532 (M+1, ES+).

30 **Example 287**

**2-[1-(3,4-dimethoxy-benzyl)-5-(3-fluoro-propoxy)-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**



prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with 1-bromo-3-fluoro-propane

LC-MS: *rt* = 0.62 min, 538 (*M*+1, ES+).

5

#### Example 288

**2-[1-(3,4-dimethoxy-benzyl)-5-(2-fluoro-ethoxy)-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

10 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with 1-bromo-2-fluoro-ethane

LC-MS: *rt* = 0.59 min, 524 (*M*+1, ES+).

15

#### Example 289

**2-[1-(3,4-dimethoxy-benzyl)-5-(2,2-difluoro-ethoxy)-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

20 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with 1-bromo-2,2-difluoro-ethane

LC-MS: *rt* = 0.61 min, 542 (*M*+1, ES+).

#### Example 290

25

**[2-[(Pyridin-2-yl-methyl)-carbamoyl-methyl]-1-(3,4-dimethoxy-benzyl)-8-methoxy-1,2,3,4-tetrahydro-isoquinolin-5-yloxy]-acetic acid methyl ester:**

30 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-5-hydroxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with methyl bromoacetate

LC-MS: *rt* = 0.58 min, 550 (*M*+1, ES+).

**Example 291**

2-[1-(3,4-dimethoxy-benzyl)-8-ethoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with ethyl iodide  
LC-MS: rt = 0.62 min, 506 (M+1, ES+).

**Example 292**

2-[1-(3,4-dimethoxy-benzyl)-8-propoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with propyl bromide

LC-MS: rt = 0.66 min, 520 (M+1, ES+).

**Example 293**

2-[1-(3,4-dimethoxy-benzyl)-8-allyloxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with allyl bromide

LC-MS: rt = 0.63 min, 518 (M+1, ES+).

**Example 294**

**2-[1-(3,4-dimethoxy-benzyl)-8-isopropoxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

5 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide with isopropyl bromide

LC-MS: rt = 0.64 min, 520 (M+1, ES+).

10

**Example 295**

15 **2-[1-(3,4-dimethoxy-benzyl)-8-butoxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide with butyl bromide

20 LC-MS: rt = 0.69 min, 534 (M+1, ES+).

**Example 296**

25 **2-[1-(3,4-dimethoxy-benzyl)-8-isobutoxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(pyridin-2-yl-methyl)-acetamide with 1-bromo-2-methyl-propane

LC-MS: rt = 0.69 min, 534 (M+1, ES+).

30

**Example 297**

**2-[1-(3,4-dimethoxy-benzyl)-8-(but-2-oxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

5 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with 2-bromo-butane

LC-MS: rt = 0.68 min, 534 (M+1, ES+).

10 **Example 298**

**2-[1-(3,4-dimethoxy-benzyl)-8-(cyclopropyl-methoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

15 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with cyclopropyl-methyl bromide

LC-MS: rt = 0.66 min, 532 (M+1, ES+).

20 **Example 299**

**2-[1-(3,4-dimethoxy-benzyl)-8-cyclohexyloxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

25 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with cyclohexyl bromide

LC-MS: rt = 0.73 min, 560 (M+1, ES+).

**Example 300**

30 **2-[1-(3,4-dimethoxy-benzyl)-8-(3-fluoro-propoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with 1-bromo-3-fluoro-propane

LC-MS: *rt* = 0.62 min, 538 (M+1, ES+).

5

### Example 301

2-[1-(3,4-dimethoxy-benzyl)-8-(2-fluoro-ethoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

10

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with 1-bromo-2-fluoro-ethane

LC-MS: *rt* = 0.59 min, 524 (M+1, ES+).

15

### Example 302

2-[1-(3,4-dimethoxy-benzyl)-8-(2,2-difluoro-ethoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

20

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide with 1-bromo-2,2-difluoro-ethane

LC-MS: *rt* = 0.62 min, 542 (M+1, ES+).

### Example 303

25

2-[1-(4-ethoxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:

prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with ethyl iodide

30

LC-MS: *rt* = 3.9 min, 505 (M+1, ES+).

**Example 304**

**2-[1-(4-propoxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

5 prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with propyl bromide  
LC-MS: *rt* = 4.2 min, 519 (*M*+1, ES+).

**Example 305**

10

**2-[1-(4-butoxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with butyl bromide  
15 LC-MS: *rt* = 4.4 min, 533 (*M*+1, ES+).

**Example 306**

20

**2-[1-(4-allyloxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with allyl bromide  
LC-MS: *rt* = 4.0 min, 517 (*M*+1, ES+).

25

**Example 307**

**2-[1-(4-isopropoxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with isopropyl bromide  
30 LC-MS: *rt* = 4.0 min, 519 (*M*+1, ES+).

**Example 308**

2-[1-(4-isobutoxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-  
5 isoquinolin-2-yl]-*N*-benzyl-acetamide:

prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-  
dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with 1-bromo-2-methyl-  
propane

LC-MS: rt = 4.5 min, 533 (M+1, ES+).

**Example 309**

2-[1-(4-(cyclopropyl-methoxy)-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-  
15 1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:

prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-  
dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with cyclopropyl-methyl  
bromide

20 LC-MS: rt = 4.2 min, 531 (M+1, ES+).

**Example 310**

{4-[2-(Benzylcarbamoyl-methyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-  
25 isoquinolin-1-ylmethyl]-2-methoxy-phenoxy}-acetic acid ethyl ester

prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-  
dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with ethyl bromoacetate

LC-MS: rt = 3.9 min, 563 (M+1, ES+).

**Example 311**

**2-[1-(3-ethoxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

5 prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with ethyl iodide

LC-MS: *rt* = 3.8 min, 505 (M+1, ES+).

**Example 312**

10

**2-[1-(3-propoxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

15 prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with propyl bromide

LC-MS: *rt* = 4.1 min, 519 (M+1, ES+).

**Example 313**

20

**2-[1-(3-allyloxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with allyl bromide

25 LC-MS: *rt* = 4.0 min, 517 (M+1, ES+).

**Example 314**

30

**2-[1-(3-isopropoxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**



prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with isopropyl bromide  
LC-MS: *rt* = 4.0 min, 519 (*M*+1, ES+).

5        **Example 315**

**2-[1-(3-butoxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide:**

10        prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with butyl bromide  
LC-MS: *rt* = 4.3 min, 533 (*M*+1, ES+).

15

**Example 316**

**2-{1-[3-(but-2-oxy)-4-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-benzyl-acetamide:**

20        prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with 2-bromo-butane  
LC-MS: *rt* = 4.2 min, 533 (*M*+1, ES+).

**Example 317**

25

**2-{1-[3-(cyclopropyl-methoxy)-4-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-benzyl-acetamide:**

30        prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with cyclopropyl-methyl bromide  
LC-MS: *rt* = 4.0 min, 531 (*M*+1, ES+).

**Example 318**

**2-{1-[3-(3-fluoro-propoxy)-4-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with 1-bromo-3-fluoro-propane  
LC-MS:  $t_r = 3.9$  min, 537 (M+1, ES+).

**Example 319**

**2-[1-(3,4-dimethoxy-benzyl)-7-(1-methyl-prop-2-oxy)-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide:**

At room temperature *tert.*-butyl 2,2,2-trichloroacetimidate (437 mg, 0.36 mL, 2.0 mmol) was added to a solution of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide (95.3 mg, 0.2 mmol) in dichloromethane (5.0 mL) and cyclohexane (5.0 mL). The reaction mixture was treated with a solution of boron trifluoride diethyl etherate (50  $\mu$ L, 0.4 mmol) in 10 mL dichloromethane and stirred for 22 h. Another portion of *tert.*-butyl 2,2,2-trichloroacetimidate (244 mg, 0.20 mL, 1.1 mmol) was added. After stirring for three days a saturated solution of NaHCO<sub>3</sub> (10 mL), water (10 mL) and ethyl acetate (40 mL) were added, the phases were separated and the aqueous phase was extracted three times with ethyl acetate (30 mL). The combined organic phases were concentrated in vacuo and purified by flash-chromatography to give the titled product (80.4 mg, 75%) as pale yellow oil.

LC-MS:  $t_r = 4.2$  min, 533 (M+1, ES+).

**C.3 Reaktion of Phenols with Heteroaryl chlorides or Heteroaryl-methyl sulfones (general procedure):**

A solution of the respective heteroaryl chloride or methyl-sulfone in DMF (1.0 mL, 0.20 M) was added to a mixture of the respective phenol (0.15 mmol) and

K<sub>2</sub>CO<sub>3</sub> (75 mg). The reaction mixture was stirred at 100°C for 16 h. Water (2.0 mL) and ethyl acetate (2.0 mL) were added, the phases were separated and the aqueous phase was extracted two times with ethyl acetate. The combined organic phases were concentrated in vacuo to give the following tetrahydroisoquinoline derivatives:

#### Example 320

**2-{1-[3-(pyrimidin-2-yloxy)-4-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl}-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with 2-chloro-pyrimidine  
LC-MS: rt = 0.60 min, 555 (M+1, ES+).

#### Example 321

**2-{1-[4-(pyrimidin-2-yloxy)-3-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl}-N-benzyl-acetamide:**

prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-benzyl-acetamide with 2-chloro-pyrimidine  
LC-MS: rt = 0.60 min, 555 (M+1, ES+).

#### Example 322

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(pyrimidin-2-yloxy)-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1H-isoquinolin-2-yl]-N-(indan-1-yl)-acetamide with 2-chloro-pyrimidine  
LC-MS: rt = 3.81 min, 581 (M+1, ES+).

**Example 323**

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(5-methoxy-pyrimidin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-methane-sulfonyl-5-methoxy-pyrimidine

LC-MS: *rt* = 0.69 min, 611 (M+1, ES+).

**Example 324**

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(4,6-dimethyl-pyrimidin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-methane-sulfonyl-4,6-dimethyl-pyrimidine

LC-MS: *rt* = 0.70 min, 609 (M+1, ES+).

**Example 325**

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(5-bromo-pyrimidin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 5-bromo-2-chloro-pyrimidine

LC-MS: *rt* = 0.74 min, 659 (M+1, ES+).

**Example 326**

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(5-methyl-pyrimidin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-chloro-5-methylpyrimidine

LC-MS: rt = 0.68 min, 595 (M+1, ES+).

5

### Example 327

10

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(4,6-dimethoxy-pyrimidin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-methane-sulfonyl-4,6-dimethoxy-pyrimidine

15

LC-MS: rt = 0.75 min, 641 (M+1, ES+).

### Example 328

20

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(5-trifluoromethyl-pyrimidin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-methane-sulfonyl-5-trifluoromethyl-pyrimidine

25

LC-MS: rt = 0.77 min, 649 (M+1, ES+).

### Example 329

30

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(5-chloro-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2,5-dichloro-pyridine  
LC-MS: *rt* = 0.77 min, 614 (M+1, ES+).

5

**Example 330**

10

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(5-trifluoromethyl-pyridin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-chloro-5-trifluoromethyl-pyridine

15

LC-MS: *rt* = 0.80 min, 648 (M+1, ES+).

**Example 331**

20

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(4-trifluoromethyl-pyrimidin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-chloro-4-trifluoromethyl-pyrimidine

25

LC-MS: *rt* = 0.77 min, 649 (M+1, ES+).

**Example 332**

30

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(2,6-dimethoxy-pyrimidin-4-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 4-chloro-2,6-dimethoxy-pyrimidine

LC-MS: *rt* = 0.76 min, 641 (*M*+1, ES+).

5

#### Example 333

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(pyrazin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

10

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-chloro-pyrazine

LC-MS: *rt* = 0.68 min, 581 (*M*+1, ES+).

#### Example 334

15

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(thiazol-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 2-bromo-thiazole

20

LC-MS: *rt* = 0.72 min, 586 (*M*+1, ES+).

#### C.4 Reaktion of Phenols with Carbamoylchlorides (general procedure):

25

A solution of the respective phenol (0.20 mmol) and triethylamine (0.30 mL, 2.15 mmol) in THF (1.0 mL) was treated with the respective carbamoylchloride (2.2 mmol) and stirred at reflux for 16 h. Water (2.0 mL) and ethyl acetate (2.0 mL) were added, the phases were separated and the aqueous phase was extracted two times with ethyl acetate. The combined organic phases were concentrated in vacuo to give the following tetrahydroisoquinoline derivatives:

30

**Example 335**

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(*N,N*-dimethylcarbamoyloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

5 prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with *N,N*-dimethylcarbamoyl chloride

LC-MS: *rt* = 0.74 min, 574 (*M*+1, *ES*<sup>+</sup>).

**Example 336**

10

**2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(4-morpholine-carbonyloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

prepared by reaction of 2-[1-(3,4-dimethoxy-benzyl)-7-hydroxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide with 4-morpholinecarbonyl chloride

15

LC-MS: *rt* = 0.72 min, 616 (*M*+1, *ES*<sup>+</sup>).

**Example 337**

20

**2-{1-[4-Methoxy-3-(*N,N*-dimethylcarbamoyloxy)-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-benzyl-acetamide:**

prepared by reaction of 2-[1-(3-hydroxy-4-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with *N,N*-dimethyl-carbamoyl chloride

25

LC-MS: *rt* = 0.62 min, 548 (*M*+1, *ES*<sup>+</sup>).

**Example 338**

30

**2-{1-[3-Methoxy-4-(*N,N*-dimethylcarbamoyloxy)-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-benzyl-acetamide:**



prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with *N,N*-dimethyl-carbamoyl chloride

LC-MS: *rt* = 0.63 min, 548 (*M*+1, ES+).

5

#### Example 339

2-{1-[3-Methoxy-4-(4-morpholine-carbonyloxy)-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-benzyl-acetamide:

10 prepared by reaction of 2-[1-(4-hydroxy-3-methoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide with 4-morpholine-carbonyl chloride

LC-MS: *rt* = 0.61 min, 590 (*M*+1, ES+).

#### 15 D Coupling of 1-Hydroxymethyl-substituted Tetrahydroisoquinolines with Nitrogen-nucleophiles (general procedure):

To a solution of 2-(1-Hydroxymethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(indan-1-yl)-acetamide (0.10 mmol) and diisopropylethyl-amine (0.25 mmol) in THF (0.50 mL) was added a solution of methanesulfonyl chloride in THF (0.25 mL, 0.44 M). After 60 min the reaction mixture was treated with a solution of the respective nitrogen-nucleophile in THF (0.25 mL, 0.48 M) and stirred for 18 h. Water (2.0 mL) and ethyl acetate (2.0 mL) were added, the phases were separated and the aqueous phase was extracted two times with ethyl acetate.  
25 The combined organic phases were concentrated in vacuo to give the following tetrahydroisoquinoline derivatives:

#### Example 340

30 2-[1-(5,6-Dimethyl-benzimidazol-1-ylmethyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:

prepared by reaction of 2-(1-Hydroxymethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(indan-1-yl)-acetamide with 5,6-dimethylbenzimidazole  
LC-MS: *rt* = 0.64 min, 525 (*M*+1, *ES*+).

5        **Example 341**

**2-[1-(1,2,3,4-Tetrahydroisoquinolin-2-ylmethyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide:**

10       prepared by reaction of 2-(1-Hydroxymethyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl)-*N*-(indan-1-yl)-acetamide with 1,2,3,4-tetrahydro-isoquinoline  
LC-MS: *rt* = 0.71 min, 512 (*M*+1, *ES*+).

15       **E.       General procedure for the preparation of the isonitrile derivatives**

Isonitriles (or isocyanides) have been prepared by reaction of the *N*-alkyl-formamides (formed by reaction of the corresponding amine with formic ethyl ester) with POCl<sub>3</sub>.

20

25

30

### Abbreviations:

5

	BSA	Bovine serum albumine
10	CHO	Chinese hamster ovary
	DMF	Dimethylformamide
	DMSO	Dimethylsulfoxide
	ES	Electron spray
	FCS	Foetal calf serum
15	FLIPR	Fluorescent imaging plate reader
	HBSS	Hank's balanced salt solution
	HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
	MeOH	Methanol
	MS	Mass spectroscopy
20	LC	Liquid chromatography

25

30

PyBOP      Benzotriazole-1-yl-oxy-tris-pyrrolidino-  
Phosphoniumhexafluorophosphate

R<sub>f</sub>          Retention front

5      R<sub>t</sub>          retention time

RT          Room temperature

THF          Tetrahydrofuran

10

15

20

25

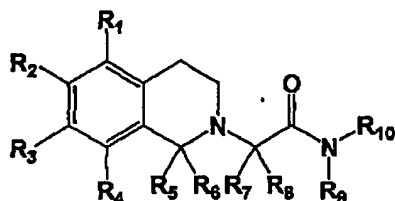
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## Claims

### 1. Compounds of the general formula (I)



formula (I)

wherein:

$R^1, R^2, R^3, R^4$  independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclylalkyloxy,  $R^{11}CO-$ ,  $NR^{12}R^{13}CO-$ ,  $R^{12}R^{13}N-$ ,  $R^{11}OOC-$ ,  $R^{11}SO_2NH-$  or  $R^{14}-CO-NH-$  or  $R^2$  and  $R^3$  together as well as  $R^1$  and  $R^2$  together and  $R^3$  and  $R^4$  together may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms;

$R^5, R^6, R^7, R^8, R^9, R^{10}$  independently represent hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{11}$  represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{12}$  and  $R^{13}$  independently represent hydrogen, alkyl, cycloalkyl, aryl, aralkyl,

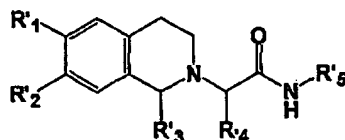
heterocyclyl or heterocyclyl-lower alkyl;

$R^{14}$  represents alkyl, aryl, cycloalkyl, heterocyclyl,  $R^{12}R^{13}N-$  or  $R^{11}O-$ .

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

## 2. Compounds of the general formula (II)

5



General formula II

10

wherein:

$R^1$  and  $R^2$  independently represent hydrogen, hydroxy, methoxy or halogen or may form with the phenyl ring a five, six or seven membered-ring containing one or two oxygen atoms,

15  $R^3$ ,  $R^4$ ,  $R^5$  independently represent aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl.

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

20

3. Specific compounds of general formula I:

2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

25 2-[1-(3,4-dimethoxy-benzyl)-8-(cyclopropyl-methoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-(2-fluoro-ethoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

30

2-[1-(3,4-dimethoxy-benzyl)-8-(2,2-difluoro-ethoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-ethoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

35

2-[1-(3,4-dimethoxy-benzyl)-8-propoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

- 5 2-[1-(3,4-dimethoxy-benzyl)-8-allyloxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-isopropoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

10

2-[1-(3,4-dimethoxy-benzyl)-5-propoxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

4. Specific compounds of formula II:

- 15 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-naphthalen-1-ylmethyl-acetamide

- 20 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide

25

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(pyrazin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

- 30 2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(thiazol-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(5-methoxy-indan-1-yl)-acetamide

- 35 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-methoxy-indan-1-yl)-acetamide

- 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-methyl-indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(4-methyl-indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-methoxy-indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-methyl-indan-1-yl)-acetamide
- 2-{1-[4-(pyrimidin-2-yloxy)-3-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl}-*N*-benzyl-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(*N,N*-dimethylcarbamoyloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(3-fluoro-propoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(2-fluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(2,2-difluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(but-2-oxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(cyclopropyl-methoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide



2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(indan-1-yl)-acetamide

5 2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
(indan-1-yl)-acetamide

10 2-[1-(3,4-dimethoxy-benzyl)-7-isopropoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(indan-1-yl)-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-(1-methyl-prop-2-oxy)-6-methoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-benzyl-acetamide

15 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-[(1*S*)-indan-1-yl]-acetamide

20 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-benzyl-acetamide

2-[(1*S*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
[(1*S*)-indan-1-yl]-acetamide

25 2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
benzyl-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
benzyl-acetamide

30 2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
benzyl-acetamide

*N*-benzyl-2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
35 acetamide

2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide

*N*-benzyl-2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
5 acetamide

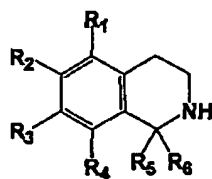
2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide

10 2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide

2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-4-yl-methyl)-acetamide

15 2-[1-(3,4-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide

5. A process for the combinatorial preparation of compounds of the general  
20 formula I, wherein  $R^6$ ,  $R^7$  and  $R^9$  are hydrogen, by using an Ugi-three-components-condensation reaction, comprising the one pot reaction of a compound of formula III



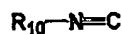
formula III

25 wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  have the meaning given in formula I above and  $R_6$  represents hydrogen,  
with a compound of formula IV



formula IV

wherein  $R_7$  represents hydrogen and  $R_8$  has the meaning given in formula I above,  
and a compound of formula V



5

formula V

wherein  $R_{10}$  has the meaning given in formula I above,

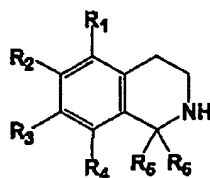
if desired, isolating pharmacologically active compounds in a manner known per se, if

10 desired, resolving a racemate obtained in a manner known per se and, if desired

converting a compound or compounds obtained into a salt in a manner known per se.

6. A process for the preparation of compounds of formula I above, comprising  
reacting a compound of formula III',

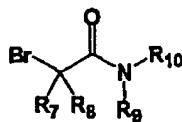
15



formula III'

20

wherein the substituents  $R_1$  to  $R_6$  have the meaning given in formula I above, with  
a compound of formula VI



25

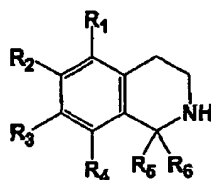
formula VI

wherein  $R_7$  to  $R_{10}$  have the meaning given in formula I above.

30

7. A process for the preparation of compounds of formula I above, comprising reacting a compound of formula III',

5

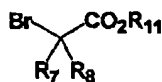


formula III'

10

wherein the substituents R<sub>1</sub> to R<sub>6</sub> have the meaning given in formula I above, with

a) a compound of formula IX



15

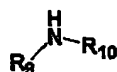
formula IX

wherein R<sub>7</sub>, R<sub>8</sub> and R<sub>11</sub> have the meaning given in formula I above,

b) cleaving an ester obtained in a manner known per se and reacting the acid formed with

20

c) a compound of formula X



formula X

wherein the substituents R<sub>9</sub> and R<sub>10</sub> have the meaning given in formula I above,

25

if desired, resolving a racemate obtained in a manner known per se and, if desired, converting a compound obtained into a salt in a manner known per se.

8. Pharmaceutical compositions for the treatment of disorders which are associated with the role of orexin, especially disorders such as obesity and sleep disorders,

30

if desired, resolving a racemate obtained in a manner known per se and, if desired, converting a compound obtained into a salt in a manner per se.

9. *Pharmaceutical compositions for the treatment of disorders which are associated with the orexin, especially disorders such as obesity and sleep disorders,*
- 5 *comprising containing a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, and usual carrier materials and adjuvants.*
10. *The compounds of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, for use as medicaments for the treatment of disorders which are*
- 10 *associated with a role of orexin, especially obesity and sleep disorders.*
11. *A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof.*
- 15 12. *A process for the manufacture of pharmaceutical compositions for the treatment of disorders associated with the role of orexin, especially obesity and sleep disorders, containing one or more compounds as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt or salts thereof, as active ingredients which process*
- 20 *comprises mixing one or more active ingredient or ingredients with pharmaceutically acceptable excipients and adjuvants in a manner known per se.*
13. *A compound as described as end-product in any one of examples 1 to 70.*
14. *The invention as hereinbefore described.*

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## INTERNATIONAL SEARCH REPORT

National Application No.

PCT/EP 01/02733

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D217/20 C07D217/04 C07D401/12 A61K31/435 A61P3/04  
A61P25/20

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, PAJ, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 480 714 A (WERNER LINCOLN HARVEY) 25 November 1969 (1969-11-25) see formula (II) and (III) column 2 example 2  --- -/-	1,2,8-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*A\* document member of the same patent family

Date of the actual completion of the international search

25 July 2001

Date of mailing of the international search report

09/08/2001

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Schmid, J-C

## INTERNATIONAL SEARCH REPORT

International Application No  
PC1/EP 01/02733

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 109, no. 19, 7 November 1988 (1988-11-07) Columbus, Ohio, US; abstract no. 170679, KHALMURATOV, KH. A. ET AL: "Synthesis of substituted aminoacetyl derivatives of 2,5-2,7- diaminofluorene" XP002172557 RN 116306-56-0 2(1H)-Isoquinolineacetamide, N,N'- 9H-fluorene-2,7-diylbis(3,4-dihydro-6,7- dimethoxy-1-methyl-, 'S-(R*,R*)!- and RN 116306-52-6 abstract & UZB. KHIM. ZH. (1988), (1), 34-6,	1,2,8-10
X	LUKEVICS, E. ET AL: "Silyl modification of biologically active compounds. 4. Derivatives of amino acids in the tetrahydroquinoline, tetrahydroisoquinoline, and tetrahydroislaquinoline series" CHEM. HETEROCYCL. COMPD. (N. Y.) (1997), 33(2), 234-238, XP001008092 see compound IIc	1,8-10
X	WO 98 23593 A (CHANG GEORGE ;PFIZER (US); QUALLICH GEORGE JOSEPH (US)) 4 June 1998 (1998-06-04) claims 1,27-29; examples 80-84	1,8-10
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 09, 31 July 1998 (1998-07-31) & JP 10 095766 A (SANWA KAGAKU KENKYUSHO CO LTD), 14 April 1998 (1998-04-14) abstract	1,8-10
X	PATENT ABSTRACTS OF JAPAN vol. 010, no. 214 (C-362), 25 July 1986 (1986-07-25) & JP 61 053268 A (HOKURIKU SEIYAKU CO LTD), 17 March 1986 (1986-03-17) RN 103918-89-4 2(1H)-Isoquinolineacetamide, 3,4-dihydro- N-'2-'(4-methylphenyl)amino!carbonyl!phen yl! abstract	1,8-10
	-/-	

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 01/02733

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>PATENT ABSTRACTS OF JAPAN vol. 1996, no. 02, 29 February 1996 (1996-02-29) &amp; JP 07 267961 A (TAISHO PHARMACEUT CO LTD), 17 October 1995 (1995-10-17) see formula I RN 173456-86-5 2(1H)-Isoquinolineacetamide, 3,4-dihydro- N-'3-(1,4-dihydro-4-oxobenzofuro'3,2-d! pyrimidin-2-yl)-4-ethoxyphenyl!</p>	1,8-10
X	<p>CHEMICAL ABSTRACTS, vol. 110, no. 23, 5 June 1989 (1989-06-05) Columbus, Ohio, US; abstract no. 205079, SAITKULOV, A. M. ET AL: "Interferon-inducing activity of fluorenone derivatives" XP002172558 RN-116306-56-0 2(1H)-Isoquinolineacetamide, N,N'-9H-fluorene-2,7-diylbis'3,4-dihydro- 6,7-dimethoxy-1-methyl-, 'S-(R*,R*)!- abstract &amp; UZB. BIOL. ZH. (1988), (6), 5-9,</p>	1,8-10
X	<p>CHEMICAL ABSTRACTS, vol. 110, no. 19, 8 May 1989 (1989-05-08) Columbus, Ohio, US; abstract no. 173523, AUELBEKOV, S. A. ET AL: "Reaction of 2,7-bis(chloroacetyl-amino)fluoren-9-one with amines" XP002172559 RN 117823-92-4 2(1H)-Isoquinolineacetamide, N,N'-(9-oxo-9H-fluorene-2,7-diyl)bis'3,4- dihydro-6-hydroxy-7-methoxy-1-methyl-, 'S-(R*,R*)!- abstract &amp; UZB. KHIM. ZH. (1988), (3), 23-6,</p>	1,8-10

-/-



## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/EP 01/02733

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 110, no. 1, 2 January 1989 (1989-01-02) Columbus, Ohio, US; abstract no. 459, KHALMURATOV, KH. A. ET AL: "DNA complexes with derivatives of fluorene and fluorenone having interferon-inducing activity" XP002172560 RN 117823-92-4 2(1H)-Isoquinolineacetamide, N,N'- (9-oxo-9H-fluorene-2,7-diyl)bis[3,4- dihydro-6-hydroxy-7-methoxy-1-methyl-, 'S-(R*,R*)!- and RN 117823-95-7 & KHIM. PRIR. SOEDIN. (1988), (3), 404-9,	1,8-10
X	HAZEBROUCQ, GEORGES: "2,3,4,5-Tetrahydro-1H-3-benzazepin-1-ones and hexahydroimidazoisquinolines" ANN. CHIM. (PARIS) (1966), 1(5/6), 221-54, XP001007459 see compound 47 page 247	1
X	KEMPTER, G. ET AL: "Synthesis of heteroanalogs of piperidinoacetanilides" WISS. Z. - MARTIN-LUTHER-UNIV. HALLE-WITTENBERG, MATH.-NATURWISS. REIHE (1983), 32(5), 3-25, XP000943458 page 12 -page 15; tables 6,7	1
X	DD 204 917 B (SCHELLONG HARTMUT;BARTH ALFRED; JUMAR ALFRED; KEMPTER GERHARD; ZEIGER) 14 December 1983 (1983-12-14) examples 7,9	1
X	EP 0 494 623 A (GLAXO LAB SA) 15 July 1992 (1992-07-15) see formula (VI), (VII) page 9 see intermediates 57,58,65,66 page 34 -page 36	1
X	DD 261 158 A (UNIV HALLE WITTENBERG) 19 October 1988 (1988-10-19) see formula III example 2	1
	-/-	

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/02733

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 68, no. 1, 1 January 1968 (1968-01-01) Columbus, Ohio, US; abstract no. 2798, HORI, MIKIO ET AL: "Benzaza cycloalkane derivatives. IV" XP002172561 RN 17133-65-2 2(1H)-Isoquinolineacetanilide, 3,4-dihydro-.alpha.-methyl- abstract & GIFU YAKKA DAIGAKU KIYO (1966), NO. 16, 68-70,	1
X	DD 258 817 A (UNIV HALLE WITTENBERG) 3 August 1988 (1988-08-03) see formula III page 2; example 2	1
P,X	WO 01 02368 A (LAUFFER DAVID ;LEDFO BRIAN (US); VERTEX PHARMA (US); MULLICAN MI) 11 January 2001 (2001-01-11) page 28; claims; example 2	1,8-10
P,X	WO 00 35882 A (ASTRAZENECA UK LTD ;FORST JANET MARIE (US); CHEN DEBORAH WENG CHUN) 22 June 2000 (2000-06-22) see formula XXII page 8 page 57 -page 59; examples 96,100,110	1,8-10
P,X	WO 00 29399 A (BOEHRINGER INGELHEIM CA LTD ;SIMONEAU BRUNO (CA); FAUCHER ANNE MAR) 25 May 2000 (2000-05-25) page 64; example 408	1,8-10
P,X	WO 00 78744 A (ASTRAZENECA UK LTD ;FORST JANET MARIE (US); CHEN DEBORAH WENG CHUN) 28 December 2000 (2000-12-28) see formula IV page 12 see method 3 page 33 page 36; example 31	1
P,X	WO 00 78742 A (ASTRAZENECA UK LTD ;FORST JANET MARIE (US); CHEN DEBORAH WENG CHUN) 28 December 2000 (2000-12-28) see formula (XIV) page 12 page 32; examples 28,31	1
	-/-	

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 01/02733

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WO 99 58533 A (JOHNS AMANDA ;PORTER RODERICK ALAN (GB); SMITHKLINE BEECHAM PLC (G) 18 November 1999 (1999-11-18) the whole document</p> <p>-----</p>	1-12

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 13,14

In view of the large number of the individually claimed compounds and also in view of the wording of claim 13 referring to the description, which renders it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search of this claim is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely for the compounds of claim 1.

Claim 14 is not clear in scope.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/02733

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(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
20 September 2001 (20.09.2001)

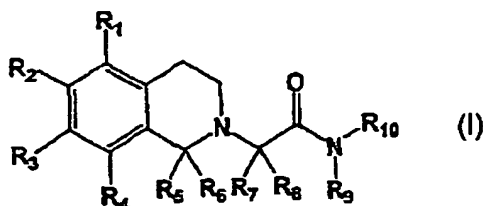
PCT

(10) International Publication Number  
**WO 01/68609 A1**

- (51) International Patent Classification<sup>7</sup>: C07D 217/20, 217/04, 401/12, A61K 31/435, A61P 3/04, 25/20
- (74) Agent: HOFMANN, Dieter; StratAll, Therwilerstrasse 87, CH-4153 Reinach (CH).
- (21) International Application Number: PCT/EP01/02733
- (22) International Filing Date: 12 March 2001 (12.03.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
PCT/EP00/02245 14 March 2000 (14.03.2000) EP
- (71) Applicant (for all designated States except US):  
ACTELION PHARMACEUTICALS LTD. [CH/CH];  
Gewerbestrasse 16, CH-4123 Allschwil (CH).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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- (72) Inventors; and
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(54) Title: 1,2,3,4-TETRAHYDROISOQUINOLINE DERIVATIVES



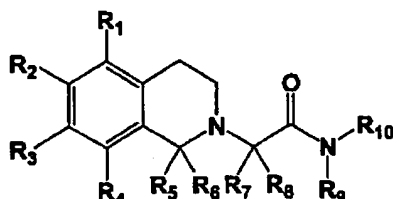
(57) Abstract: The invention relates to novel 1,2,3,4-tetrahydroisoquinoline derivatives of formula (I) and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as orexin receptor antagonists.

## AMENDED CLAIMS

[received by the International Bureau on 28 September 2001 (28.09.01);  
original claims 1-14 replaced by amended claims 1-11 (9 pages)]

## 1. Compounds of the general formula (I)

5



formula (I)

10 wherein:

$R^1, R^2, R^3, R^4$  independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclylalkyloxy,  $R^{11}CO-$ ,  $NR^{12}R^{13}CO-$ ,  $R^{12}R^{13}N-$ ,  $R^{11}OOC-$ ,  $R^{11}SO_2NH-$  or

15  $R^{14}-CO-NH-$  or  $R^2$  and  $R^3$  together as well as  $R^1$  and  $R^2$  together and  $R^3$  and  $R^4$  together may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms;

$R^5$  represents aryl, aralkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

20  $R^6$  represents hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^7$  and  $R^8$  independently represent hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^9$  represents aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, 25 heterocyclyl or heterocyclyl-lower alkyl;

$R^{10}$  represents hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{11}$  represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{12}$  and  $R^{13}$  independently represent hydrogen, alkyl, cycloalkyl, aryl, aralkyl, 30 heterocyclyl or heterocyclyl-lower alkyl;

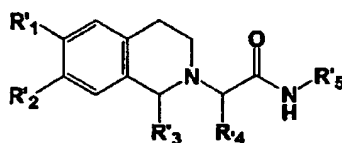


$R^{14}$  represents alkyl, aryl, cycloalkyl, heterocyclyl,  $R^{12}R^{13}N$ - or  $R^{11}O$ -.

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

5

## 2. Compounds of the general formula (II)



10

General formula II

wherein:

$R'^1$  and  $R'^2$  independently represent hydrogen, hydroxy, lower alkoxy or halogen or may form with the phenyl ring a five, six or seven membered-ring containing one or two oxygen atoms,

$R'^3$  represents aryl, aralkyl, lower alkenyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R'^4$  represents hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R'^5$  represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

## 3. A compound according to any of claims 1 to 2, selected from the group consisting of

2-[1-(3,4-Dimethoxy-benzyl)-5,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-(cyclopropyl-methoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-(2-fluoro-ethoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

5 2-[1-(3,4-dimethoxy-benzyl)-8-(2,2-difluoro-ethoxy)-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-ethoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

10

2-[1-(3,4-dimethoxy-benzyl)-8-propoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

15

2-[1-(3,4-dimethoxy-benzyl)-8-allyloxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

2-[1-(3,4-dimethoxy-benzyl)-8-isopropoxy-5-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

20

2-[1-(3,4-dimethoxy-benzyl)-5-propoxy-8-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide:

25

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-naphthalen-1-ylmethyl-acetamide

30

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide

35

2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(pyrazin-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide

- 2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(thiazol-2-yloxy)-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
5 *N*-(5-methoxy-indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(6-methoxy-indan-1-yl)-acetamide
- 10 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(6-methyl-indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl)-acetamide
- 15 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
*N*-(4-methyl-indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-  
20 methoxy-indan-1-yl)-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(6-  
methyl-indan-1-yl)-acetamide
- 25 2-{1-[4-(pyrimidin-2-yloxy)-3-methoxy-benzyl]-6,7-dimethoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl}-*N*-benzyl-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-6-methoxy-7-(*N,N*-dimethylcarbamoyloxy)-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 30 2-[1-(3,4-dimethoxy-benzyl)-7-(3-fluoro-propoxy)-6-methoxy-3,4-dihydro-1*H*-  
isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(2-fluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-  
35 2-yl]-*N*-(indan-1-yl)-acetamide

- 2-[1-(3,4-dimethoxy-benzyl)-7-(2,2-difluoro-ethoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(but-2-oxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
5 *N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(cyclopropyl-methoxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 10 2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 15 2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-isopropoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-  
20 *N*-(indan-1-yl)-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-(1-methyl-prop-2-oxy)-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide
- 25 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide
- 2-[1-(3,4-Dimethoxy-benzyl)-6-methoxy-7-isopropoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide
- 30 2-[(1*S*)-1-(3,4-Dimethoxy-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide
- 2-[1-(3,4-dimethoxy-benzyl)-7-ethoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-  
35 benzyl-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-propoxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

2-[1-(3,4-dimethoxy-benzyl)-7-allyloxy-6-methoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-benzyl-acetamide

*N*-benzyl-2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetamide

2-[1-(3,4-Dimethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-[(1*S*)-indan-1-yl]-acetamide

*N*-benzyl-2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetamide

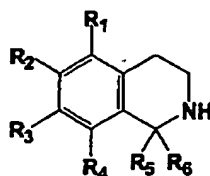
2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-2-yl-methyl)-acetamide

2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide

2-[1-(3,4-Diethyl-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-4-yl-methyl)-acetamide

2-[1-(3,4-Dichloro-benzyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-*N*-(pyridin-3-yl-methyl)-acetamide

4. A process for the combinatorial preparation of compounds of the general formula I, wherein R<sup>6</sup>, R<sup>7</sup> and R<sup>9</sup> are hydrogen, by using an Ugi-three-components-  
condensation reaction, comprising the one pot reaction of a compound of formula III

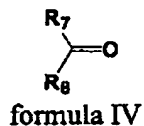


formula III

wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$  and  $R_5$  have the meaning given in formula I above and  $R_6$  represents hydrogen,

with a compound of formula IV

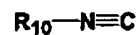
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wherein  $R_7$  represents hydrogen and  $R_8$  has the meaning given in formula I above,

10

and a compound of formula V



formula V

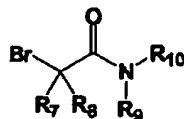
15 wherein  $R_{10}$  has the meaning given in formula I above,  
if desired, isolating pharmacologically active compounds in a manner known per se, if  
desired, resolving a racemate obtained in a manner known per se and, if desired  
converting a compound or compounds obtained into a salt in a manner known per se.

20 5. A process for the preparation of compounds of formula I above, comprising  
reacting a compound of formula III',



formula III'

25 wherein the substituents  $R_1$  to  $R_6$  have the meaning given in formula I above, with  
a compound of formula VI

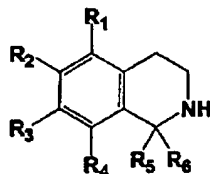


formula VI

wherein  $R_7$  to  $R_{10}$  have the meaning given in formula I above.

5

6. A process for the preparation of compounds of formula I above, comprising reacting a compound of formula III',

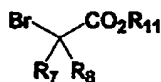


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formula III'

wherein the substituents  $R_1$  to  $R_6$  have the meaning given in formula I above, with

a) a compound of formula IX



15

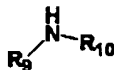
formula IX

wherein  $R_7$ ,  $R_8$  and  $R_{11}$  have the meaning given in formula I above,

b) cleaving an ester obtained in a manner known per se and reacting the acid formed with

20

c) a compound of formula X



formula X

25 wherein the substituents  $R_9$  and  $R_{10}$  have the meaning given in formula I above, if desired, resolving a racemate obtained in a manner known per se and, if desired, converting a compound obtained into a salt in a manner known per se.

7. Pharmaceutical compositions for the treatment of disorders which are associated  
30 with the role of orexin, especially disorders such as obesity and sleep disorders,

containing a compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, and usual carrier materials and adjuvants.

8. The compounds of any one of claims 1 to 3, or a pharmaceutically acceptable  
5 salt thereof, for use as medicaments for the treatment of disorders which are associated with a role of orexin, especially obesity and sleep disorders.

9. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need  
10 thereof an effective amount of a compound as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof.

10. A process for the manufacture of pharmaceutical compositions for the treatment of disorders associated with the role of orexin, especially obesity and sleep disorders,  
15 containing one or more compounds as claimed in any one of claims 1 to 3, or a pharmaceutically acceptable salt or salts thereof, as active ingredients which process comprises mixing one or more active ingredient or ingredients with pharmaceutically acceptable excipients and adjuvants in a manner known per se.

20 11. A compound as described as target compound in any one of examples 1 to 341.

25

30

35